IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PAR PHARMACEUTICAL, INC., PAR STERILE PRODUCTS, LLC, and ENDO PAR INNOVATION COMPANY, LLC, *Plaintiffs*, v. EAGLE PHARMACEUTICALS INC., *Defendant*.	C.A. No. 18-823-CFC-JLH
PAR PHARMACEUTICAL, INC., PAR STERILE PRODUCTS, LLC, and ENDO PAR INNOVATION COMPANY, LLC, *Plaintiffs*, v. AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, et al., *Defendants*.	C.A. No. 18-2032-CFC-CJB

PAR'S PROPOSED FINDINGS OF FACT REGARDING VALIDITY AND ENFORCEABILITY OF THE '209 AND '785 PATENTS

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OF COUNSEL:

Martin J. Black
Sharon K. Gagliardi
Brian M. Goldberg

Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
FARNAN LLP
919 North Market St.
12th Floor
Wilmington, DE 19801
Tel: 302-777-0300

Luke M. Reilly
Daniel R. Roberts
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
Tel: (215) 994-4000
martin.black@dechert.com
sharon.gagliardi@dechert.com
brian.goldberg@dechert.com
luke.reilly@dechert.com
daniel.roberts@dechert.com

Robert D. Rhoad
DECHERT LLP
502 Carnegie Center, Suite 104
Princeton, NJ 08540-7814
Tel: (609) 955-3200
robert.rhoad@dechert.com

Jonathan D. J. Loeb, Ph.D
DECHERT LLP
2400 W. El Camino Real, Suite 700
Mountain View, CA 94040-1499
Tel: (650) 813-4995
jonathan.loeb@dechert.com

Blake B. Greene
DECHERT LLP
300 W. 6th Street, Suite 2010
Austin, TX 78701
Tel: (512) 394-3000
blake.greene@dechert.com

Fax: 320-777-0301
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Attorneys for Plaintiffs Par Pharmaceuti
Inc., Par Sterile Products, LLC, and End
Par Innovation Company, LLC

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

Abbreviation	Description
API	Active pharmaceutical ingredient
DCOL	Defendants' Proposed Conclusions of Law on Invalidity and Unenforceability
DFF	Defendants' Proposed Findings of Fact Regarding Invalidity and Unenforceability
FOF	Par's Proposed Findings of Fact Regarding Validity and Enforceability of the '209 and '785 Patents
Infringement FOF	Par's Proposed Findings of Fact Regarding Eagle's Infringement of the '209 and '785 Patents
Infringement Br.	Par's Post-Trial Brief Regarding Eagle's Infringement of the '209 and '785 Patents

Plaintiffs Par Pharmaceutical, Inc., Par Sterile Products, LLC, and Endo Par Innovation Company, LLC (collectively, "Par") respectfully submit their proposed Findings of Fact Regarding Validity and Enforceability of the '209 and '785 Patents.

I. THE PARTIES[1]

137. Plaintiff Par Pharmaceutical, Inc. ("Par Pharmaceutical") is a corporation organized and existing under the laws of the State of New York, having a principal place of business at 1 Ram Ridge Road, Chestnut Ridge, New York 10977. Par Pharmaceutical develops, manufactures, and markets pharmaceutical products in the United States. D.I. 268 (No. 18-823), *Par v. Eagle* Pretrial Order (hereinafter "Eagle PTO"), Ex. 1 ¶ 1; D.I. 282 (No. 18-2032), *Par v. Amneal* Pretrial Order (hereinafter "Amneal PTO"), Ex. 1 ¶ 1.

138. Plaintiff Par Sterile Products, LLC ("Par Sterile Products") is a limited liability company organized and existing under the laws of Delaware, having its principal place of business at 1 Ram Ridge Road, Chestnut Ridge, New York 10977. Par Sterile Products develops, manufactures, and markets injectable pharmaceutical products, and provides manufacturing services to the

[1] Par has continued the numbering used in its Infringement FOF. Additionally, Par has duplicated certain Findings of Fact presented in its Infringement FOF because Defendant Amneal is not a party to Par's infringement case against Eagle.

biopharmaceutical and pharmaceutical industry. Eagle PTO Ex. 1 ¶ 2; Amneal PTO Ex. 1 ¶ 2.

139. Plaintiff Endo Par Innovation Company ("EPIC") is a limited liability company organized and existing under the laws of Delaware, having its principal place of business at 1 Ram Ridge Road, Chestnut Ridge, New York 10977. Eagle PTO Ex. 1 ¶ 3; Amneal PTO Ex. 1 ¶ 3.

140. Plaintiffs Par Pharmaceutical, Par Sterile Products, and EPIC are referred to collectively as "Par." Eagle PTO Ex. 1 ¶ 4; Amneal PTO Ex. 1 ¶ 4.

141. Defendant Eagle ("Eagle") is a corporation organized under the laws of the State of Delaware having a principal place of business at 50 Tice Road, Suite 315, Woodcliff, New Jersey, 07677. Eagle develops and markets pharmaceutical products, including injectable pharmaceutical products, in the United States. Eagle PTO Ex. 1 ¶ 5.

142. Defendant Amneal EU, Limited ("Amneal EU") is a limited liability company organized and existing under the laws of the Switzerland, having its principal place of business at Turmstrasse 30 6312, Steinhausen, Switzerland. Amneal EU develops, manufactures, markets and distributes pharmaceutical products, including injectable pharmaceutical products, for sale in the State of Delaware and throughout the United States. Amneal PTO Ex. 1 ¶ 5.

143. Defendant Amneal Pharmaceuticals of New York, LLC ("Amneal New York") is a limited liability company organized and existing under the laws of the State of Delaware having its principal place of business at 50 Horseblock Road, Brookhaven, New York 11719. Amneal New York develops, produces, and distributes pharmaceutical products, including injectable pharmaceutical products, for sale in the State of Delaware and throughout the United States. Amneal PTO Ex. 1 ¶ 6.

144. Defendant Amneal Biosciences, LLC ("Amneal Biosciences") is a limited liability company organized and existing under the laws of the State of Delaware having its principal place of business at 400 Crossing Boulevard, Floor 3, Bridgewater, New Jersey 08807. Amneal Biosciences distributes pharmaceutical products, including injectable pharmaceutical products, for sale in the State of Delaware and throughout the United States. Amneal PTO Ex. 1 ¶ 7.

145. Defendant Amneal Pharmaceutical PVT. LTD. ("Amneal PVT") is a limited liability company organized and existing under the laws of the India having a principal place of business at Plot No. 15, PHARMEZ Special Economic Zone, Sarkhej-Bavia N.H., No. 8A, Vil.: Matoda, Tal.:Sanand, Ahmedabad, Gujarat, 382213, India. Amneal India manufactures, packages, tests, and ships pharmaceutical products to the United States. Amneal PTO Ex. 1 ¶ 8.

146. Defendants Amneal EU, Amneal New York, Amneal Biosciences, and Amneal PVT are referred to collectively as "Amneal." Amneal PTO Ex. 1 ¶ 9.

II. BACKGROUND

147. Vasopressin is a peptide drug that causes contraction of vascular and other smooth muscle cells. Eagle PTO Ex. 1 ¶ 6; Amneal PTO Ex. 1 ¶ 10.

148. The Asserted Patents are directed to improved vasopressin formulations, particularly in terms of stability. *See, e.g.*, Tr. 198:25-199:8, 766:17-24 (Kirsch); JTX-2 at 53:56-59. The patents provide advantages in stability primarily through the identification of pH 3.7-3.9 as the pH range of optimal stability. Tr. 199:9-17 (Kirsch).

149. pH is a measure of the concentration of hydronium ions, which are protonated water molecules which give rise to the acidity of an aqueous solution (e.g., the higher the concentration of hydronium ions, the greater the acidity of the solution). Tr. 200:20-201:8 (Kirsch). pH is a logarithmic scale, meaning that even small differences between pH values have a substantial difference in the concentration of acid in the solution. Tr. 201:12-202:6 (Kirsch). As Dr. Kirsch explained, "in going from a pH of 3.8 to a pH of 3.6, we would see almost a 60 percent increase in acid concentration. And even for a tenth of a pH unit, going, say, from pH 3.7 to 3.6, the concentration of acid would increase by over 25 percent." *Id.*

150. pH can affect the stability of drug molecules. Tr. 201:9-11 (Kirsch).

151. Peptide drugs like vasopressin are particularly susceptible to various types of instability processes, in terms of physical and chemical instability. Tr. 197:24-198:9 (Kirsch). Drugs can undergo chemical instability pathways or chemical changes, such as hydrolysis, oxidation, isomerization, polymerization, and photochemical decomposition, throughout the drug product life cycle, which includes API synthesis and storage, product manufacturing, shipping, storage, and administration. Tr. 202:7-203:7 (Kirsch). Dr. Kirsch explained the effect of those pathways: "what happens is as they degrade, the drug potency is lost as the drug degrades. The levels of impurity will increase as well. And so this can have an impact on the safety and efficacy of the drug product." *Id.*

152. Vasopressin has long been used in critical care situations to treat, among other things, dangerously low blood pressure for patients in septic shock and post-cardiotomy shock. Tr. 125:16-127:17 (Coralic); 494:7-496:10 (Cross).

153. JHP Pharmaceuticals, LLC ("JHP") sold a vasopressin product under the tradename Pitressin for years prior to 2014.[2] DTX-38.5; Tr. 390:16-391:5 (Park). Because vasopressin products were sold prior to adoption of the Federal Food, Drug and Cosmetics Act, 21 U.S.C. ch. 9, § 301, et seq., JHP was not

[2] On February 20, 2014, Par Pharmaceutical Companies, Inc. acquired JHP, and then on February 26, 2014, JHP changed its name to Par Sterile Products, LLC. Eagle PTO Ex. 1 ¶ 8; Amneal PTO Ex. 1 ¶ 15.

required to obtain FDA-approval to make and sell Pitressin, and sold it as an unapproved drug product. DTX-38.5; DTX-25.9; *see also* DFF¶27, 30.

III. PAR'S VASOSTRICT® PRODUCTS

A. Par's Original VASOSTRICT® Product

154. On September 25, 2012, JHP submitted NDA No. 204485 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, seeking approval from the FDA for a vasopressin injection product to increase blood pressure in adults with vasodilatory shock. Eagle PTO Ex. 1 ¶ 7; Amneal PTO Ex. 1 ¶ 14.

155. On April 17, 2014, FDA approved NDA No. 204485. The trade name for the approved vasopressin product was VASOSTRICT®. Eagle PTO Ex. 1 ¶ 9; Amneal PTO Ex. 1 ¶ 16.

156. The Vasostrict product as originally approved in April 2014 had a shelf life of 12 months at room temperature storage. Eagle PTO Ex. 1 ¶ 10. Par never sold Vasostrict with the April 2014 Vasostrict Label that was approved at that time—i.e., with the 12 month room temperature shelf life. *See* Tr. 719:2-7 (Kannan), 814:6-25 (Kirsch).

157. Par filed a supplement to its NDA (204485/S-001) seeking approval for storage between 2°C and 8°C and change in shelf-life expiration—to 24 months at refrigerated storage; FDA approved that supplement (NDA 204485/S-001) on September 18, 2014. Eagle PTO Ex. 1 ¶ 11. Vasostrict was first sold and offered

for sale in November 2014, with the approved September 2014 label. Eagle PTO Ex. 1 ¶¶ 12, 16; Amneal PTO Ex. 1 ¶ 18.

158. Par subsequently filed a second supplement to its NDA (204485/S-002) seeking approval for room temperature storage for up to 12 months following removal from storage at refrigerated conditions; FDA approved that supplement (NDA 204485/S-002) on May 7, 2015. Eagle PTO Ex. 1 ¶ 13; *see* Amneal PTO Ex. 1 ¶ 17.

159. Throughout the trial, the parties referred to the formulation as described in NDA 204485, and the supplements approved on April 17, 2014, September 18, 2014, and May 7, 2015 as "Original Vasostrict." Eagle PTO Ex. 1 ¶ 14; Amneal PTO Ex. 1 ¶ 17.

B. Par's Reformulated VASOSTRICT® Product

160. After Vasostrict was originally approved with a 12-month room temperature shelf life, in addition to seeking a longer shelf life under refrigerated conditions, Par also undertook a project to reformulate Vasostrict to obtain a more stable product that could support a longer room temperature shelf life. *See, e.g.*, DTDX-2 (Kannan 2019 Tr.) 54:8-54:20, 70:14-71:2, 156:15-157:5; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12; Tr. 714:10-23 (Kannan). Through their research efforts, the Par inventors determined that the pH 3.7-3.9 range achieved stability advantages that were unexpected in view of the prior art. *See, e.g.*,

DTDX-4 (Kenney 2020 Tr.) 214:19-22, 215:9-15, 215:18-216:11; DTX-1115.14; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12, 182:18-182:23, 183:7-14, 185:21-25, 186:2-188:6; DTDX-10 (Sanghvi 2020 Tr.) 115:25-116:1, 116:4-5, 116:10-16; DTDX-7 (Vandse 2019 Tr.) 152:20-153:15; DTDX-3 (Kenney 2019 Tr.) 218:23-219:8, 219:10-12; DTDX-9 (Sanghvi 2019 Tr.) 152:10-18; Tr. 827:10-13 (Kirsch).

161. Based on that work, Par Sterile Products filed a further supplement to its NDA (204485/S-003) seeking approval for a new 1 mL formulation of Vasostrict. Changes to the formulation of Vasostrict in this supplement included addition of a sodium acetate buffer and a change in pH—from 3.4 to 3.6 in Original Vasostrict to 3.8 in Reformulated Vasostrict. On March 18, 2016, FDA approved NDA 204485/S-003. Eagle PTO Ex. 1 ¶ 17; Amneal PTO Ex. 1 ¶ 20.

162. The data obtained by Par for Reformulated Vasostrict showed improvements as compared to Original Vasostrict, in terms of both higher vasopressin assay[3] values and lower impurity levels. *See, e.g.*, DTDX-3 (Kenney 2019 Tr.) 89:8-13, 89:16-18, 89:20-21; DTDX-4 (Kenney 2020 Tr.) 217:3-17, 217:19-21, 219:19-24, 220:20-221:7; DTDX-7 (Vandse 2019 Tr.) 152:20-153:15, 251:22-252:6; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12; Tr. 797:12-799:19 (Kirsch).

[3] "Assay" refers to the amount of vasopressin. *See, e.g.*, Tr. 185:21-22 (Aungst).

163. Moreover, Par obtained data sufficient to support an 18-month room temperature shelf life for Reformulated Vasostrict, which was longer than the shelf life that could be supported for Original Vasostrict. *See, e.g.*, DTDX-2 (Kannan 2019 Tr.) 235:18-22, 235:24-236:5, 297:9-298:5, 298:8-298:13; DTDX-3 (Kenney 2019 Tr.) 87:15-88:5; DTDX-4 (Kenney 2020 Tr.) 154:14-15, 154:17-25, 217:3-17, 217:19-21, 219:19-24, 220:20-221:7; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12; Tr. 799:20-800:4, 888:5-17 (Kirsch); *compare* PTX-252 at PAR-VASO_0030582 *with* DTX-53.19.

164. Par Sterile Products also filed an additional supplement to its NDA (204485/S-004) seeking approval for a 10 mL multi-dose formulation of Vasostrict with the same concentration of vasopressin as the 1 mL formulation (i.e., 20 units of vasopressin/mL). On December 17, 2016, FDA approved NDA 204485/S-004. Eagle PTO Ex. 1 ¶ 18; Amneal PTO Ex. 1 ¶ 21.

165. The parties refer to the current formulation of Vasostrict—approved on March 18, 2016 and December 17, 2016—as "Reformulated Vasostrict." Eagle PTO Ex. 1 ¶ 19; Amneal PTO Ex. 1 ¶ 22.

166. Par Sterile Products is the holder of NDA No. 204485 for Vasostrict, including all supplements thereto. Eagle PTO Ex. 1 ¶ 24; Amneal PTO Ex. 1 ¶ 26.

IV. THE PATENTS-IN-SUIT

167. Par obtained patents based on the above-described research and development work it performed in connection with the development of Reformulated Vasostrict, including: (1) U.S. Patent No. 9,750,785 (the "'785 Patent"), and (2) U.S. Patent No. 9,744,209 (the "'209 Patent") (collectively the "Asserted Patents"). JTX-2; JTX-3; Tr. 766:18-767:4, 775:16-776:10, 837:1-22, 838:20-840:9 (Kirsch).

168. Par Pharmaceutical is the assignee and owner of the Asserted Patents. EPIC is the exclusive licensee of the '209 and '785 patents. Eagle PTO Ex. 1 ¶ 31; Amneal PTO Ex. 1 ¶ 33.

169. The '209 and '785 patents have the same specification. JTX-2; JTX-3; Tr. 200:6-19 (Kirsch).

A. The Asserted Claims

170. Par asserts claims 1, 5, and 8 of the '785 patent against both Eagle and Amneal. Eagle PTO Ex. 1 ¶ 36; Amneal PTO Ex. 1 ¶ 38. Each asserted '785 patent claim is directed to specified vasopressin compositions. JTX-3.

171. The Asserted Claims of the '785 patent recite the following:

> **Claim 1**: A pharmaceutical composition comprising, in a unit dosage form, from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof, wherein the unit dosage form further comprises impurities that are present in an amount of 0.9% to 1.7%, wherein the impurities have from about 85% to about 100%

sequence homology to SEQ ID NO.: 1, and wherein the unit dosage form has a pH of 3.7-3.9.

Claim 5: The pharmaceutical composition of claim 1, wherein the impurities comprise SEQ ID NO.: 4, and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

Claim 8: The pharmaceutical composition of claim 1, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3% and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

JTX-3.

172. Par asserts claims 1, 4, 5, and 7 of the '209 patent against Eagle and claims 1-2 and 4-8 against Amneal. Eagle PTO Ex. 1 ¶ 35; Amneal PTO Ex. 1 ¶ 37. Each asserted '209 patent claim is directed to methods of treatment using specified vasopressin compositions. JTX-2.

173. In particular, the asserted claims of the '209 patent recite the following:

Claim 1: A method of increasing blood pressure in a human in need thereof, the method comprising administering to the human a unit dosage form, wherein the unit dosage form comprises from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically acceptable salt thereof, wherein:

the unit dosage form has a pH of 3.7-3.9;

the unit dosage form further comprises impurities that are present in an amount of 0.9% - 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1;

the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute

to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute; and

the human is hypotensive.

Claim 2: The method of claim 1, wherein the impurities comprise SEQ ID NO.: 2, and SEQ ID No.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3%.

Claim 4: The method of claim 1, wherein the impurities comprise SEQID NO.: 4, and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

Claim 5: The method of claim 1, wherein the impurities comprise SEQ ID NO.: 7, and SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%.

Claim 6: The method of claim 1, wherein the impurities comprise SEQ ID NO.: 10, and SEQ ID No.: 10 is present in the unit dosage form in an amount of 0.1%.

Claim 7: The method of claim 1, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3% and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

Claim 8: The method of claim 7, wherein the impurities further comprise SEQ ID NO.: 3, SEQ ID NO.:7 and SEQ ID NO.: 10, and SEQ ID No.:3 is present in the unit dosage form in an amount of 0.1%, SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%, and SEQ ID NO.: 10 is present in the unit dosage form in an amount of 0.1%.

JTX-2.

174. Claims 1, 5, and 8 of the ’785 patent and claims 1-2 and 4-8 of the ’209 patent are referred to collectively as the “Asserted Claims.” The following demonstrative illustrates the Asserted Claims asserted against each Defendant:

	Eagle	Amneal
’209 Patent	1, 4, 5, 7	1, 2, 4-8
’785 Patent	1, 5, 8	1, 5, 8

175. The dependent claims of the Asserted Patents recite specific impurities of vasopressin. Tr. 205:21-206:13, 206:19-207:17 (Kirsch); JTX-2 at Tables 1, 3, claims 2, 4-8; JTX-3 at Tables 1, 3, claims 5, 8.

176. As defined in the Asserted Patents:

- SEQ ID NO.: 1 refers to vasopressin;
- SEQ ID NO.: 2 refers to Gly9-vasopressin (Gly9);
- SEQ ID NO.: 3 refers to Asp5-vasopressin (Asp5);
- SEQ ID NO.: 4 refers to Glu4-vasopressin (Glu4);
- SEQ ID NO.: 7 refers to Acetyl-vasopressin (Acetyl);
- SEQ ID NO.: 10 refers to D-Asn-vasopressin (D-Asn).

Amneal PTO Ex. 1 ¶ 39; *see* Eagle PTO Ex. 1 ¶ 42 (p. 8).

177. The Asserted Claims require a "pH of 3.7-3.9." JTX-2 at claim 1; JTX-3 at claim 1. This is referred to herein as the "pH limitation" of the Asserted Claims.

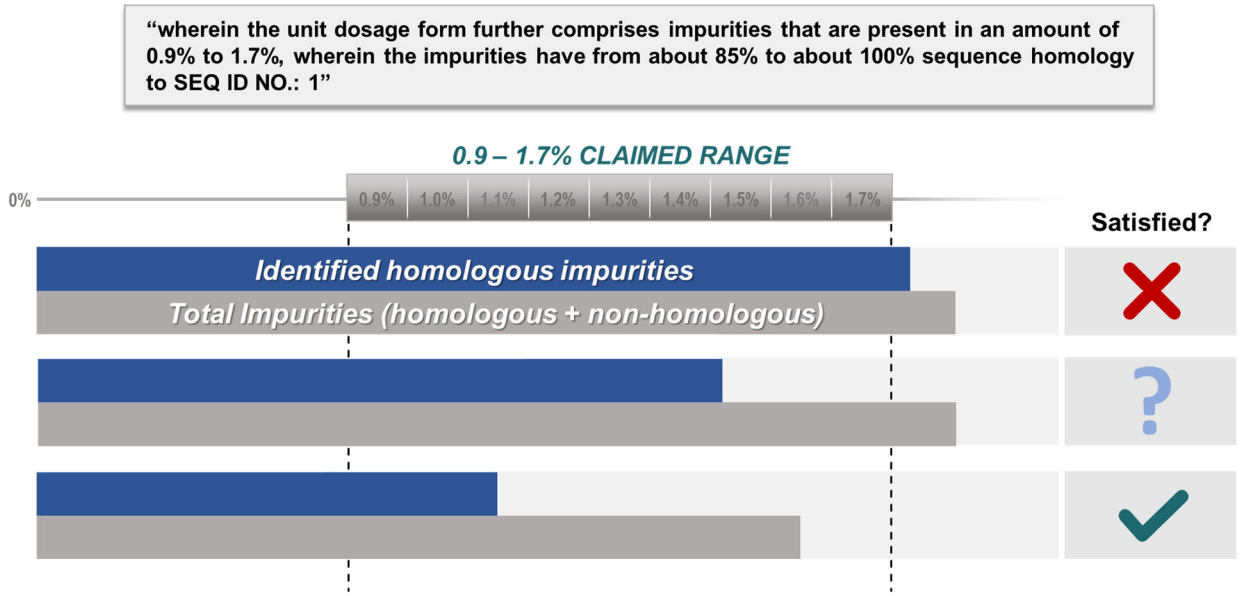
178. The Asserted Claims require "impurities that are present in an amount of 0.9% to 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1." JTX-2 at claim 1; JTX-3 at claim 1. Dependent claims 2 and 4-8 of the '209 patent and dependent claims 5 and 8 of the '785 patent further narrow the amount of certain impurities present. JTX-2 at claims 2, 4-8; JTX-3 at claims 5, 8. These limitations are referred to herein collectively as the "impurity limitations" of the Asserted Claims.

179. Determining whether an impurity has from about 85% to about 100% sequence homology ("the claimed sequence homology") to SEQ ID NO.: 1 involves identifying the impurity and comparing its sequence to SEQ ID NO.: 1, which is vasopressin. Tr. 818:25-820:19 (Kirsch). One can then add up the sum of the levels of impurities having the claimed sequence homology to determine whether the 0.9-1.7% range of claim 1 of the Asserted Patents is satisfied. Tr. 820:10-19 (Kirsch). An impurity whose identity is unknown may or may not have the claimed sequence homology. Tr. 820:20-821:2 (Kirsch). Where the identity of every impurity is not known, such as in the case of Defendants' asserted prior art, there are ways to determine whether the claim 1 impurity limitation is satisfied

using the levels of identified impurities with the claimed sequence homology ("identified homologous impurities") and total impurities, for example:

> Where the identified homologous impurities and the total impurities are both above or below the claimed 0.9-1.7% range, the claim 1 impurity limitation is not met;
>
> Where the identified homologous impurities are within the claimed 0.9-1.7% range and the total impurities are above the claimed range, the claim 1 impurity limitation may or may not be met; and
>
> Where the identified homologous impurities and the total impurities are both within the claimed 0.9-1.7% range, the claim 1 impurity limitation is met.

Tr. 820:20-821:15 (Kirsch). Dr. Kirsch used the following demonstrative to explain these concepts:



PDX6-34.

180. Claim 1 of the '785 patent provides: "A pharmaceutical composition . . . wherein the unit dosage form has a pH from 3.7-3.9." JTX-3. Claim 1 of the '209 patent provides: "A method of increasing blood pressure in a human in need

thereof, the method comprising administering to the human a unit dosage form . . . wherein: the unit dosage form has a pH of 3.7-3.9[.]" JTX-2. Based on a plain reading of the claim language, the pH limitation of the Asserted Claims can be met at any time during the shelf life of the vasopressin formulation. Tr. 212:2-213:4 (Kirsch). This reading is also supported by the file histories of the '209 and '785 patents, in which the applicant stated: "The present claims are narrowly drawn around the results of Examples 14 and 15 in the specification, which describe that a 20 U/mL vasopressin formulation prepared at pH 3.8 was tested for impurity levels over a 15-month study period. Tables 53 and 54 provide the results of the 15-month study. The Tables indicate that the pH fluctuated between 3.7 and 3.9 over the study period . . . ." *See* PTX-843 at PAR-VASO_0005816 (citation omitted); PTX-844 at PAR-VASO_0009721; Tr. 839:4-840:3 (Kirsch).

181. Claim 1 of the '785 patent provides: "A pharmaceutical composition . . . wherein the unit dosage form further comprises impurities that are present in an amount of 0.9% to 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO. 1, and wherein the unit dosage form has a pH of 3.7-3.9." JTX-3. Claim 1 of the '209 patent provides: "A method of increasing blood pressure in a human in need thereof, the method comprising administering to the human a unit dosage form . . . wherein: the unit dosage form has a pH of 3.7-3.9; the unit dosage form further comprises impurities that are

present in an amount of 0.9% - 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO. 1[.]" JTX-2. The asserted dependent claims of the '785 and '209 patents provide: "The [pharmaceutical composition / method] of claim 1, wherein the impurities [further] comprise [a specified amount of a specified impurity (or impurities)]." JTX-2 at claims 2, 4-8; JTX-3 at claims 5, 8. Based on a plain reading of the claim language, the pH and impurity limitations (both independent and dependent) of the Asserted Claims need to be met concurrently during the shelf life of the vasopressin formulation. Tr. 213:5-214:2, 805:20-806:13 (Kirsch).

V. THE COURT'S CLAIM CONSTRUCTIONS

182. In the *Eagle* case, the parties stipulated that the claim term "vasopressin" should be construed to mean "arginine vasopressin as described in SEQ. ID. NO. 1 (see, e.g., '239 patent, cols. 25-26)" with respect to each of the Asserted Patents. D.I. 61 (No. 18-823) at 12; *see also* Eagle PTO Ex. 1 ¶ 54. Similarly, in the *Amneal* case, the Court ordered that the claim term "vasopressin" in all of the Asserted Claims should be construed to mean "arginine vasopressin as described in SEQ. ID. NO. 1." D.I. 105 (No. 18-2032) at 2.

183. In the *Eagle* case, the Court ordered that the '209 patent claim term "administering to the human a unit dosage form" be given its "[p]lain and ordinary meaning; no construction necessary." D.I. 71 (No. 18-823). In the *Amneal* case,

the parties stipulated that the Court's claim constructions in the *Eagle* case shall apply in that litigation as well. *See* D.I. 179 (No. 18-2032). In the *Amneal* case, the Court also ordered that the claim term "the unit dosage form has a pH of 3.7-3.9" in claim 1 of the Asserted Patents be given its "ordinary meaning." D.I. 105 (No. 18-2032) at 2.

184. No other claim term of the Asserted Patents was construed by the Court. Eagle PTO Ex. 1 ¶ 55; Amneal PTO Ex. 1 ¶ 48.

VI. VALIDITY

A. Defendants' "Minutes" Theory

185. In DFF¶61, Defendants contend that "Par considers the full scope of the Asserted Claims to include a vasopressin formulation that, even though manufactured to a pH outside the claimed range of 3.7-3.9, including between 3.4 and 3.6, exhibits the claimed pH at any point during its shelf life, even for just a few minutes." This contention ("Defendants' 'minutes' theory") is repeated throughout Defendants' Proposed Findings of Fact and underlies a number of their proposed findings. *See, e.g.*, DFF¶¶157, 182, 194-195, 212, 214, 220. Defendants' "minutes" theory is not based on Par's infringement case, which does not rely on any argument that Eagle's ANDA product falls within the claimed range for only a few minutes. *See, e.g.*, Infringement FOF101-104 (evidence of infringement in Eagle's registration batches as early as 10 months in a 24 month

shelf life), Infringement FOF112-116 (evidence of sufficient upward pH drift in Eagle's "optimized" batches for infringement within one month of release); *see generally* Infringement Post-Trial Br. Rather, it is based on cross-examination testimony of Par's expert Dr. Kirsch, in which he was asked a ***legal question*** of whether a hypothetical situation would constitute infringement:

> **Q**. All right. And it also – I think is it your view that if [Eagle's ANDA product] went to 3.7 to 3.9 for five minutes, that that would be infringing?
>
> **A**. Well, that's – yes I mean, I think literally, that would be infringing, yes.

Tr. 300:14-18 (Kirsch). Thus, Defendants' main invalidity attacks are based on a hypothetical infringement scenario of Defendants' creation rather than the prior art of record.

B. Person Having Ordinary Skill In The Art ("POSA")

186. The parties' respective experts (Drs. Kirsch and Park) proposed definitions of a person of ordinary skill in the art to which the Asserted Patents are directed ("POSA") that they acknowledge are very similar. *See, e.g.*, Tr. 388:20-389:1 (Dr. Park testifying that his and Dr. Kirsch's definitions are "not that different"). Their respective proposals are as follows:

- Par's Proposal: A POSA would have a Master's, Pharm.D., or Ph.D. in the field of pharmaceutical sciences or a related discipline and several years of experience in the development of pharmaceutical dosage forms. A person of ordinary skill in the art may also have less formal education and a greater among of experience. Further, a POSA would have had access to and would have worked in collaboration with persons who have

several years of experience in the formulation of drug products as well as other professionals in the drug development field, such as pharmacologists, chemists, biologists, or clinicians. Tr. 210:22-211:14 (Dr. Kirsch's definition);

- Defendants' Proposal: A person of ordinary skill in the art is someone who has a master's degree, or a PhD degree in pharmaceutical sciences or related skill with several years of experience in developing pharmaceutical dosage forms, including stable aqueous peptide formulations and more experience may substitute for lower level of education and vice-versa. Also, a person can have access to and collaboration with persons having drug formulation experience, as well as pharmacologists, chemists, biologists or clinicians. Basically, can work as a team. Tr. 388:5-19 (Dr. Park's definition).

187. Both side's experts testified that their opinions would not change if the Court were to adopt the other side's definition. Tr. 388:20-389:1 (Park); 211:19-212:1, 827:14-25 (Kirsch). Therefore, the Court need not make an express finding as to which party's definition of a POSA it will use.

C. State of the Prior Art

188. The priority date of the Asserted Claims is February 7, 2017. Tr. 389:2-6 (Park), 806:20-23 (Kirsch); *see also* DFF¶55.

189. Vasopressin products were known in the prior art to be stable, safe, and efficacious. Tr. 806:24-807:5, 826:24-827:3 (Kirsch).

190. The prior art taught that certain vasopressin products had a pH between 2.5 and 4.5. Tr. 392:10-15, 482:19-21 (Park), 812:23-813:8 (Kirsch); DTX-135.4; DTX-246.1.

191. The stability of a vasopressin product with a known pH range of 2.5-4.5 was not considered to be a problem in the prior art. Tr. 813:9-12 (Kirsch); *see also* DFF¶29. In fact, Dr. Park testified that a POSA would understand from the disclosure of pH of 2.5-4.5 in the USP monograph for Vasopressin Injection that if the pH is maintained between 2.5 and 4.5, the vasopressin product "should be good for the shelf life." Tr. 392:21-393:1, 393:14-24; DTX-135.3-4.

192. Neither the stability of Original Vasostrict nor the stability of Pitressin was a recognized problem to be solved in the prior art. Tr. 807:6-9 (Kirsch).

193. A POSA would not have known anything more about the pH of prior art vasopressin products beyond what was published. Tr. 813:13-16 (Kirsch), 486:6-17 (Park).

194. The published pH of Pitressin was 3.6. Tr. 807:13-808:1, 824:21-825:1 (Kirsch); PTX-146 at EAGLEVAS0014352.

195. The published pH of Original Vasostrict was 3.4-3.6. Tr. 482:15-18 (Park), 613:19-24 (Chyall), 807:13-21 (Kirsch); DTX-132.5; *see also* DFF¶¶38, 88.

196. The pH of vasopressin formulations was believed to have been optimized in the prior art. Tr. 807:6-9 (Kirsch). Specifically, the prior art taught that pH 3.4-3.6 was the optimal range for stability. *See, e.g.*, Tr. 807:13-808:1, 812:8-17 (Kirsch); PTX-146 at EAGLEVAS0014352-353; PTX-309 at PAR-

VASO_0238742; DTX-132.5; DTX-173.4. The published pH 3.4-3.6 range of Original Vasostrict and the published pH 3.6 value of Pitressin were within this optimal range. Tr. 807:13-808:1, 812:8-17 (Kirsch); DTX-132.5; PTX-146 at EAGLEVAS0014352.

197. M. Bi & J. Singh, *Effect of buffer pH, buffer concentration and skin with or without enzyme inhibitors on the stability of [Arg^{8}]-vasopressin*, International Journal of Pharmaceutics 197:87-93 (2000) ("Bi 2000") (DTX-173) is prior art to the Asserted Patents. Eagle PTO Ex. 1, ¶ 71; Amneal PTO Ex. 1, ¶ 68. Bi 2000 was before the Patent Office during prosecution of the Asserted Patents. Amneal PTO Ex. 1, ¶ 68.

198. Biopharmaceutics Review for NDA 204485, Center for Drug Evaluation and Research (March 2013) ("FDA Biopharmaceutics Review") (PTX-146) is prior art to the Asserted Patents. Eagle PTO Ex. 1, ¶ 79; Amneal PTO Ex. 1, ¶ 75.

199. Chemistry Review(s) for NDA 204485, Center for Drug Evaluation and Research ("FDA Chemistry Review") (PTX-309) is prior art to the Asserted Patents. Eagle PTO Ex. 1, ¶ 80; Amneal PTO Ex. 1, ¶ 76.

200. The impurity levels within vasopressin products were not considered a concern in the prior art. Tr. 807:10-12 (Kirsch); *see also* Tr. 144:12-15 (Coralic). In fact, both the impurities and impurity levels within vasopressin products were

not known in the prior art. Tr. 206:14-18, 807:10-12, 830:18-20, 836:1-18 (Kirsch).

D. Differences Between Original Vasostrict and the Asserted Claims

201. Defendants admit that the Asserted Claims "do not cover Original Vasostrict." DFF¶64.

202. The April 2014, September 2014, and May 2015 Vasostrict labels disclosed that the pH of Original Vasostrict was "adjusted with acetic acid to pH 3.4 – 3.6." Tr. 807:13-21, 814:6-815:6 (Kirsch); DTX-36.6; DTX-46.4; DTX-132.5; *see also* DFF¶88. Thus, the labels for Original Vasostrict did not disclose the pH limitation of the Asserted Claims. Tr. 828:3-13 (Kirsch).

203. The April 2014, September 2014, and May 2015 Vasostrict labels provided no disclosure about the impurities within Original Vasostrict. Tr. 815:7-9, 828:3-13 (Kirsch); DTX-36; DTX-46.3-4; DTX-132.4-5. Thus, the labels for Original Vasostrict did not disclose the impurity limitations of the Asserted Claims. *See id.*

204. Of the three registration batches of Original Vasostrict, Defendants' expert Dr. Park addressed just one—batch 310571. *See, e.g.*, Tr. 415:16-19 (Park), 815:17-19 (Kirsch). And of the more than 50 lots of Original Vasostrict that were sold before the priority date of the Asserted Patents, Dr. Park selected only two lots

to address—lot 788435 and lot 788436. Tr. 396:24-397:4, 410:21-25, 418:11-16 (Park), 823:15-16, 830:2-8 (Kirsch); DTX-86; DTX-1362.

1. Registration Batch 310571

205. Original Vasostrict registration batch 310571 was never on sale or in public use. Tr. 815:10-16, 822:11-17 (Kirsch). Thus, Original Vasostrict registration batch 310571 is not prior art to the Asserted Claims. *See id.*

206. The pH of Original Vasostrict registration batch 310571 was recorded as 3.5 for the initial through 12-month measurements, 3.8 for the 18-month measurement, and 3.5 for the 24-month measurement in refrigerated storage. Tr. 415:24-416:2 (Park), 815:20-816:4 (Kirsch); DTX-27.34, 36.

207. The pH 3.8 measurement for Original Vasostrict registration batch 310571 was not investigated or shown to be a valid number, and therefore it is unknown whether there was any analytical or lab error associated with the measurement. Tr. 816:5-11 (Kirsch).

208. Inventor Sanghvi testified that he could not conclude from the single pH 3.8 measurement that other batches of Original Vasostrict were likely to raise to 3.8. DTDX-9 (Sanghvi 2019 Tr.) 123:20-23, 124:2-4.

209. Every pH measurement in refrigerated storage for the other two Original Vasostrict registration batches was 3.5 or 3.6. Tr. 815:20-816:4 (Kirsch); DTX-27.34, 36, 38, 40, 42, 44.

210. Defendants' expert Dr. Park identified impurity levels for Original Vasostrict registration batch 310571 at only the initial and 3-month measurements, when it had a pH of 3.5. Tr. 415:16-416:2, 417:18-20 (Park); DTX-45.7; *see also* DFF¶¶117-123. These impurity measurements were also taken from a room temperature study, which is different than the refrigerated study from which Dr. Park identified the pH measurements for registration batch 310571. *Compare* DTX-45.7 and DFF¶117 *with* DTX-27.34, 36 and DFF¶116.

211. Defendants' expert Dr. Park did not consider the unidentified impurities when assessing whether Original Vasostrict satisfied the impurity limitation of claim 1 of the Asserted Patents. Tr. 398:25-399:4 (Park). Because an unidentified impurity may or may not have had the claimed sequence homology (Tr. 820:20-821:2 (Kirsch)), Dr. Park's calculation of the amount of impurities having the claimed sequence homology within Original Vasostrict products was speculative.

212. Thus, contrary to DFF¶117, Defendants have not shown that Original Vasostrict registration batch 310571 had "0.8 and 1.8% total impurities having between 85 and 100% sequence homology to vasopressin at the initial and three month time points, respectively[.]" Rather, 0.8% and 1.8% were the amount of identified impurities having the claimed sequence homology within registration batch 310571 for those measurements, respectively. DTX-45.7. There were also

unidentified impurities within registration batch 310571 that may or may not have had the claimed sequence homology. DTX-45.7; Tr. 820:20-821:2 (Kirsch).

213. Defendants did not establish that Original Vasostrict registration batch 310571 concurrently satisfied the impurity limitations of the asserted dependent claims and the impurity limitation of independent claim 1 of the Asserted Patents. *See, e.g.*, Tr. 416:11-417:17 (Park); DFF¶¶117-121.

214. Original Vasostrict registration batch 310571 had 0.33% and 0.35% SEQ ID NO. 10 (D-Asn) at each of the initial and three month time points at room temperature storage. DTX-45.7. Thus, through 3 months in room temperature storage, registration batch 310571 had SEQ ID NO. 10 in an amount that exceeded the 0.1% value claimed in claims 6 and 8 of the '209 patent. *Compare* DTX-45.7 *with* JTX-2 at claims 6 and 8.

215. Defendants did not evaluate the amount of impurities within Original Vasostrict registration batch 310571 when it was measured with a pH of 3.8 at the 18-month measurement in refrigerated storage. Tr. 415:16-417:17 (Park); DFF¶124. At that time, it had 2.6% identified impurities having the claimed sequence homology and 2.9% total impurities. Tr. 821:16-822:21 (Kirsch); DTX-27.33, 35. Thus, at 18 months in refrigerated storage, registration batch 310571 had impurities having the claimed sequence homology in an amount that exceeded the 0.9-1.7% range claimed in claim 1 of the Asserted Patents. *Compare* Tr.

821:16-822:21 (Kirsch) and DTX-27.33, 35 *with* JTX-2 at claim 1 and JTX-3 at claim 1; *see also* FOF179.

216. Original Vasostrict registration batch 310571 had 0.8% SEQ ID NO. 2 (Gly9) at the 18-month measurement in refrigerated storage. Tr. 821:16-822:21 (Kirsch); DTX-27.33, 35. Thus, at 18 months in refrigerated storage, registration batch 310571 had SEQ ID NO. 2 in an amount that exceeded the 0.1-0.3% range claimed in claims 2 and 7 of the '209 patent and claim 8 of the '785 patent. *Compare* Tr. 821:16-822:21 (Kirsch) and DTX-27.33, 35 *with* JTX-2 at claims 2 and 7 and JTX-3 at claim 8.

217. Original Vasostrict registration batch 310571 had 0.2% SEQ ID NO. 3 (Asp5) at the 18-month measurement in refrigerated storage. Tr. 821:16-822:21 (Kirsch); DTX-27.33, 35. Thus, at 18 months in refrigerated storage, registration batch 310571 had SEQ ID NO. 3 in an amount that exceeded the 0.1% value claimed in claim 8 of the '209 patent. *Compare* Tr. 821:16-822:21 (Kirsch) and DTX-27.33, 35 *with* JTX-2 at claim 8.

218. Original Vasostrict registration batch 310571 had 0.9% SEQ ID NO. 4 (Glu4) at the 18-month measurement in refrigerated storage. Tr. 821:16-822:21 (Kirsch); DTX-27.33, 35. Thus, at 18 months in refrigerated storage, registration batch 310571 had SEQ ID NO. 4 in an amount that exceeded the 0.2-0.4% range claimed in claims 4 and 7 of the '209 patent and claims 5 and 8 of the '785 patent.

Compare Tr. 821:16-822:21 (Kirsch) and DTX-27.33, 35 *with* JTX-2 at claims 4 and 7 and JTX-3 at claims 5 and 8.

219. Original Vasostrict registration batch 310571 had 0.4% SEQ ID NO. 10 (D-Asn) at the 18-month measurement in refrigerated storage. Tr. 821:16-822:21 (Kirsch); DTX-27.33, 35. Thus, at 18 months in refrigerated storage, registration batch 310571 had SEQ ID NO. 10 in an amount that exceeded the 0.1% value claimed in claims 6 and 8 of the '209 patent. *Compare* Tr. 821:16-822:21 (Kirsch) and DTX-27.33, 35 *with* JTX-2 at claims 6 and 8.

220. Original Vasostrict registration batch 310571 did not concurrently meet the pH and impurity limitations of the Asserted Claims. Tr. 822:11-21 (Kirsch); FOF206-219.

2. Lot 788436

221. Original Vasostrict lot 788436 was manufactured February 24, 2015. Tr. 822:22-823:13 (Kirsch); DTX-1378.38 (Original Vasostrict CoAs).

222. The pH of Original Vasostrict lot 788436 was recorded as 3.7 at the time of manufacture. Tr. 418:5-8, 486:18-24 (Park), 822:22-823:13 (Kirsch); DTX-1378.38.

223. Of the 15 commercial lots of Original Vasostrict for which there is a pH measurement at the time of manufacture, only lot 788436 had a pH that was

recorded as 3.7 or higher. Tr. 823:23-824:8 (Kirsch); DTX-1378. All other lots had a pH of 3.5 or 3.6. *See id.*

224. Defendants' expert Dr. Park did not know whether the pH 3.7 time of manufacture measurement for Original Vasostrict lot 788436 was actually pH 3.65 rounded. *See* Tr. 486:18-487:3 (Park).

225. Defendants admit that, at the time of manufacture, Original Vasostrict lot 788436 did not have 0.9-1.7% impurities having the claimed sequence homology, as required by claim 1 of the Asserted Patents. DFF¶127.

226. Defendants admit that, at the time of manufacture, Original Vasostrict lot 788436 did not have 0.1% SEQ ID NO. 3 (Asp5), as required by claim 8 of the '209 patent. DFF¶129.

227. Defendants admit that, at the time of manufacture, Original Vasostrict lot 788436 did not have 0.2-0.4% SEQ ID NO. 4 (Glu4), as required by claims 4 and 7 of the '209 patent and claims 5 and 8 of the '785 patent. DFF¶130.

228. Original Vasostrict lot 788436 had 0.2% SEQ ID NO. 10 (D-Asn) at the time of manufacture. DTX-1314.1. Thus, at the time of manufacture, lot 788436 had SEQ ID NO. 10 in an amount that exceeded the 0.1% value claimed in claims 6 and 8 of the '209 patent. *Compare* DTX-1314.1 *with* JTX-2 at claims 6 and 8.

229. Original Vasostrict lot 788436 did not concurrently meet the pH and impurity limitations of the Asserted Claims. FOF222-228.

230. Original Vasostrict lot 788436 was not sold until November 11, 2015, approximately nine months after its manufacture. Tr. 822:22-823:16 (Kirsch); DTX-1362.9.

231. There is no evidence of the pH or impurity levels of Original Vasostrict lot 788436 when it was on sale or in public use. Tr. 418:5-419:11 (Park), 822:22-823:9, 823:17-20 (Kirsch). Thus, Defendants have not shown by clear and convincing evidence that Original Vasostrict lot 788436 satisfied either the pH or impurity limitations of the Asserted Claims when it was on sale or in public use. *See id.*

3. Lot 788435

232. The pH of Original Vasostrict lot 788435 was recorded as 3.6 for each measurement over its 24-month shelf life. Tr. 414:9-14 (Park), 824:9-20, 857:20-858:2 (Kirsch); DTX-360.26; DFF¶91.

233. In DFF¶¶92-98 and ¶¶100-106, Defendants propose findings of fact about impurities within Original Vasostrict lot 788435 at the 6 and 9-month measurements, for which there was no supporting testimony at trial. These proposed findings of fact violate the Court's ruling excluding Defendants' expert Dr. Park from testifying about the impurities within lot 788435. Tr. 399:7-410:15,

414:15-415:14. Simply because the document (DTX-360) is in evidence does not allow Defendants to back-door facts into the record that the Court ruled could not come in. Indeed, Eagle's counsel was admonished by the Court for trying that once and told "to avoid doing that in the future." Tr. 414:15-415:14. Out of an abundance of caution, Par provides FOF234-238 in response to DFF¶¶92-98 and ¶¶100-106.

234. Contrary to DFF¶93, Defendants have not shown that Original Vasostrict lot 788435 had "0.7% total impurities having between 85 and 100% sequence homology to vasopressin on August 23, 2015." Rather, on that date, which corresponds to the 6-month measurement, 0.7% was the amount of identified impurities having the claimed sequence homology within lot 788435. DTX-360.25. There were also unidentified impurities within lot 788435 that may or may not have had the claimed sequence homology. *Id.* Thus, Defendants have not shown by clear and convincing evidence that lot 788435 had 0.9 to 1.7% impurities having between 85 and 100% sequence homology to vasopressin on August 23, 2015. *Compare* DTX-360.25 *with* JTX-2 at claim 1 and JTX-3 at claim 1; *see also* FOF179.

235. Defendants admit that, on August 23, 2015, Original Vasostrict lot 788435 did not have 0.1% SEQ ID NO. 3 (Asp5), as required by claim 8 of the '209 patent. DFF¶98.

236. Defendants admit that, on August 23, 2015, Original Vasostrict lot 788435 did not have 0.3-0.6% SEQ ID NO. 7 (Acetyl), as required by claims 5 and 8 of the '209 patent. DFF¶97.

237. Contrary to DFF¶101, Defendants have not shown that Original Vasostrict lot 788435 had "0.9% total impurities having between 85 and 100% sequence homology to vasopressin on December 2, 2015." Rather, on that date, which corresponds to the 9-month measurement, 0.9% was the amount of identified impurities having the claimed sequence homology within lot 788435, and there were 1.8% total impurities. DTX-360.25. There were also unidentified impurities within lot 788435 that may or may not have had the claimed sequence homology. *Id.* Thus, Defendants have not shown by clear and convincing evidence that lot 788435 had 0.9 to 1.7% impurities having between 85 and 100% sequence homology to vasopressin on December 2, 2015. *Compare* DTX-360.25 *with* JTX-2 at claim 1 and JTX-3 at claim 1; *see also* FOF179.

238. Defendants admit that, on December 2, 2015, Original Vasostrict lot 788435 did not have 0.1% SEQ ID NO. 3 (Asp5), as required by claim 8 of the '209 patent. DFF¶106.

239. Defendants admit that, on February 18, 2016, which corresponds to the 12-month measurement, Original Vasostrict lot 788435 did not have 0.1% SEQ ID NO. 3, as required by claim 8 of the '209 patent. DFF¶¶108, 114.

240. Defendants admit that, on February 18, 2016, Original Vasostrict lot 788435 did not have 0.3-0.6% SEQ ID NO. 7 (Acetyl), as required by claims 5 and 8 of the '209 patent. DFF¶113.

241. Because it never had a pH between 3.7 and 3.9, Original Vasostrict lot 788435 did not concurrently meet the pH and impurity limitations of the Asserted Claims at any time. FOF232; *see also* FOF233-240.

4. Other Lots and General Comments

242. Throughout the shelf lives of other commercial lots of Original Vasostrict, including lots 788442, 788432, 788433, and 802171, all pH measurements were recorded as 3.6 or lower. Tr. 824:9-20, 857:20-858:2 (Kirsch); DTX-360.11, 19, 23, 28.

243. Defendants contend that the release and stability specifications for Original Vasostrict encompassed the claimed pH 3.7-3.9 range. DFF¶¶89-90. Regardless of those specifications, there was no evidence of any Original Vasostrict product that had a pH of 3.7, 3.8, or 3.9 when it was on sale or in public use. *See, e.g.*, Tr. 823:21-824:5, 824:9-20 (Kirsch); FOF205, 231, 232, 242.

244. There was no evidence of any Original Vasostrict product that concurrently met the pH and impurity limitations of the Asserted Claims. *See, e.g.*, Tr. 806:14-19, 828:14-16 (Kirsch).

E. Eagle's ANDA Product Is Not the Same as Original Vasostrict

245. Although at certain points in the trial Defendants contended that Eagle's ANDA product is the same as Original Vasostrict (*see, e.g.*, Tr. 347:22-348:4 (Park)), Defendants failed to prove that they are the same product. In fact, when asked by the Court about this contention, Eagle's counsel admitted that Original Vasostrict and Eagle's ANDA product are ***not*** "exactly alike." Tr. 708:5-18.

246. Eagle's counsel also disagreed that Original Vasostrict and Eagle's ANDA product behave the exact same way with respect to the pH claim limitation. Tr. 703:7-704:3, 705:11-18. The reason for her disagreement became clear: she admitted that the manufacturing processes for Original Vasostrict and Eagle's ANDA product were not exactly the same and that the manufacturing process affects pH drift. Tr. 708:10-18.

247. Even putting aside the foregoing admissions by Eagle's counsel, Defendants' expert Dr. Park did not demonstrate that Eagle's ANDA product is the same as Original Vasostrict. Although he testified that Par's manufacturing process could affect the pH profile of its product, Dr. Park failed to analyze Par's manufacturing process for Original Vasostrict. Tr. 476:14-477:20. Dr. Park also did not know whether Eagle's ANDA product and Original Vasostrict had a different source for the API, but that if they did, they would have different

impurities in the formulation and different amounts of impurities. Tr. 478:10-23 (Park). Accordingly, there is no evidence in the record that suggests that the pH of Original Vasostrict drifts like Eagle's product.

248. There was also unrebutted evidence of the differences in stability between Eagle's ANDA product and Original Vasostrict. Tr. 801:16-21. For example, whereas the Original Vasostrict registration batches showed an average increase of 4.5% in total impurity levels across 12 months at room temperature, Eagle's registration batches SVA002 and SVA003 showed an average increase of 5.5%. Tr. 797:12-798:7, 800:20-801:5 (Kirsch).

F. No Prima Facie Case of Obviousness

249. In view of the prior art, a POSA would have expected the pH 3.4-3.6 range and the pH 3.7-3.9 range to exhibit different properties for a vasopressin formulation. Tr. 828:17-829:12, 850:7-11 (Kirsch); FOF260-269. Specifically, a POSA would have expected a vasopressin formulation within the claimed pH 3.7-3.9 range to be less stable than a formulation with a pH of 3.4-3.6. Tr. 812:8-22, 827:10-13, 836:8-16 (Kirsch); FOF260-269.

250. There is no overlap between the pH 3.4-3.6 range and the claimed pH 3.7-3.9 range. Tr. 828:17-829:1, 884:6-9 (Kirsch).

251. A POSA would have known that even small differences in pH could affect stability. Tr. 828:17-829:3 (Kirsch). Small differences in pH can result in a

substantial difference in the concentration of acid in a solution. For example, there is more than a 25% difference in the concentration of acid between pH 3.6 and pH 3.7. Tr. 201:12-202:6 (Kirsch).

252. Defendants provided no evidence that a POSA would have expected the pH 3.4-3.6 range and the pH 3.7-3.9 range to exhibit the same properties for a vasopressin formulation. *See* Tr. 411:23-412:16 (Park). Rather, Defendants' expert Dr. Park testified only about the differences in stability between (1) a formulation at pH 3.64 and one at 3.65 and (2) a formulation at pH 3.6 and one at pH 3.6 that spends five minutes at pH 3.7 (i.e., Defendants' "minutes" theory). *Id.*

253. Defendants selectively cite Dr. Kirsch's cross-examination testimony as alleged support of their statement that "[a] POSA at the Asserted Patent priority date would not have expected to be able to detect any difference between the stability of a vasopressin formulation with a pH of 3.64 . . . and that of a vasopressin formulation with a pH of 3.65[.]" DFF¶158 (citing Tr. 853:12-15, 850:25-851:5); *see also, e.g.*, DFF¶164 (citing Tr. 853:12-15), ¶166 (citing Tr. 850:25-851:5), ¶168 (citing Tr. 851:17-853:8), ¶203 (citing Tr. 853:12-15), ¶215 (citing Tr. 853:12-15, 850:25-851:16). However, Dr. Kirsch testified that a product with pH 3.64 and a product with pH 3.65 were expected to have different properties:

> **Q.** So if we factor that in, what you've suggested here is that a product with 3.64 and one with pH 3.65, you're opining that those are expected to have different properties?
>
> **A.** Yes.

Tr. 850:17-21 (Kirsch). And, he testified that under a high enough temperature, "you would see a difference" in stability between a sample at pH 3.65 compared with one at pH 3.64 that spent five minutes at pH 3.65. Tr. 852:17-853:3 (Kirsch).

254. Defendants contend that "Original Vasostrict was sold and in public use with pH 3.6 and between 0.9% and 1.7% total impurities having between 85% and 100% sequence homology to vasopressin." DFF¶153; *see also* DFF¶165 ("Original Vasostrict as sold and in public use satisfied the method of treatment, vasopressin concentration, unit dosage form, and impurities limitations of the asserted claims."). Defendants, however, have identified only a single lot of Original Vasostrict that met those criteria—that is, lot 788435 at the 12-month measurement. *See* DFF¶¶109, 115. At that time, however, lot 788435 did not have impurities that satisfied '209 patent claims 5 and 8. FOF239-240.

255. Defendants contend that "Original Vasostrict was sold and in public use at a pH of 3.6, which abuts the pH range of the asserted claims." DFF¶155. Defendants presented no evidence of any pH measurement for a commercial lot of Original Vasostrict, such as lot 788435, that was recorded to the hundredth place. *See, e.g.*, Tr. 414:9-14 (Park); DTX-360.25-26. Under standard rounding

principles, an actual pH measurement between 3.55 and 3.64 would be recorded as 3.6. *See, e.g.*, Tr. 226:13-227:13, 808:6-21 (Kirsch), 411:18-22 (Park). Any pH 3.6 measurement for lot 788435, or any other commercial lot of Original Vasostrict, therefore might have been as low as 3.55. *See id.* Thus, Defendants have not shown by clear and convincing evidence that Original Vasostrict lot 788435, or any other commercial lot of Original Vasostrict that had a recorded pH of 3.6, had a pH of 3.64, or even greater than 3.60, during its shelf life. *See* Tr. 414:9-14 (Park); DTX-360.25-26.

256. Contrary to DFF¶78, the '209 patent at column 12, lines 17-24 does not state that "Original Vasostrict contains 'acetic acid . . . quantity sufficient to bring pH to about 3.4 to about 3.6.'" There is no connection in the text between the stated formulation and Original Vasostrict. *See* JTX-2 at 12:17-24. Nor did Dr. Kirsch agree that the formulation discussed in that passage was Original Vasostrict. Rather he said he was not sure, and acknowledged what Mr. Vandse testified. Tr. 876:5-877:14 (Kirsch). Regardless, it is undisputed that Original Vasostrict was known in the prior art to have a pH of 3.4-3.6, not "about 3.4 to about 3.6." *See* Tr. 482:15-18 (Park), 613:19-24 (Chyall), 807:13-21 (Kirsch); DTX-132.5; *see also* DFF¶¶38, 88.

257. Relatedly, Defendants contend: "Dr. Kirsch previously testified that when a particular pH range follows the phrase 'about,' that pH range may be

'broader' than what rounding principles would allow. Based on Dr. Kirsch's testimony, the description of Original Vasostrict, as provided in the '209 Patent, could include a pH of 3.65 or higher." DFF¶79 (citation omitted). Defendants mischaracterize Dr. Kirsch's testimony. During cross-examination, Defendants attempted to apply Dr. Kirsch's opinion about the claim term "about" in a patent no longer at issue in this case to the word "about" that appears in the specification of the asserted '209 patent. Tr. 879:1-882:13, 884:14-20 (Kirsch). As Dr. Kirsch testified, he did not agree that "about 3.6" in the '209 patent specification meant "something more than 3.64" because there would need to be some guidance about what "about" meant in that context, for example:

> **Q.** And about 3.6. So that's something more than 3.64; right?
>
> **A.** Not necessarily. It could simply 3.64. It could be. I would need additional information to make that. There has to be some clarification about what the about meant.
>
> ***
>
> **Q.** . . . So, again, I think the baseline here is 3.6 includes 3.64?
>
> **A.** That's correct. If it simply says 3.6, that meant one would assume with rounding it meant 3.64. If it says about, then additional information is needed to understand what about means in this context.

Id. (excerpts at Tr. 881:11-15, 881:20-25). Thus, Defendants are incorrect in their contention that "there is overlap between the pH of the prior art Original Vasostrict formulation and the vasopressin formulation claimed in the asserted claims of the

Patents-in-Suit, and Dr. Kirsch's opinions to the contrary are not credible." *See* DFF¶79.

258. Contrary to DFF¶159, Defendants have not shown by clear and convincing evidence that the sale and public use of "Original Vasostrict with its label and properties . . . would have rendered the claimed methods and formulations in the Asserted Claims obvious." *See, e.g.*, Tr. 826:8-827:13, 846:24-847:5 (Kirsch).

G. No Motivation to Modify or Combine the Prior Art

259. Defendants presented no evidence that there would have been a motivation to combine or modify the prior art to achieve the claimed inventions. *See, e.g.*, Tr. 829:20-22 (Kirsch). Thus, it is undisputed that a POSA would not have been motivated to combine or modify the prior art to achieve the claimed inventions. Tr. 826:8-827:7, 829:13-22, 833:25:834:20 (Kirsch).

1. Teaching Away

260. Bi 2000 published a pH-rate profile for the degradation of vasopressin. Tr. 808:6-24 (Kirsch); DTX-173.4. Bi 2000 tested a number of pH values between pH 2.6 and 8.5, including pH 3.35, which rounds to pH 3.4, and pH 3.66, which rounds to pH 3.7 and is within the claimed pH range. Tr. 808:6-24 (Kirsch); DTX-173.2, 4. Bi 2000 found that the minimum rate of vasopressin

degradation occurred at pH 3.35 and concluded that vasopressin "is most stable at pH 3.35 among pH values tested[.]" Tr. 808:6-810:1 (Kirsch); DTX-173.4.

261. A POSA would have considered Bi 2000's teachings relevant to understanding the optimal pH for vasopressin formulations generally. Tr. 809:10-19 (Kirsch).

262. In view of Bi 2000, a POSA would have expected increasing the pH of vasopressin formulations above pH 3.4 and towards the claimed pH 3.7-3.9 range to result in decreased stability. Tr. 809:4-9 (Kirsch); DTX-173.4.

263. The FDA Biopharmaceutics Review and FDA Chemistry Review were part of FDA's review of the Original Vasostrict NDA and summarize FDA's observations from its review of the biopharmaceutics section and the chemistry and manufacturing section of the NDA. Tr. 810:5-811:10 (Kirsch); *see also* Tr. 421:11-17 (Park).

264. Dr. Park testified that a POSA would have looked to FDA publications about Original Vasostrict. Tr. 481:24-482:25 (Park).

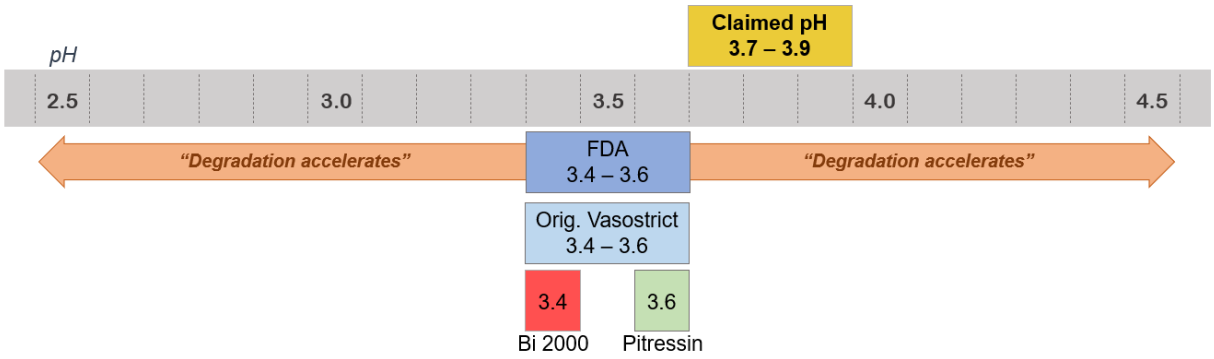
265. In the FDA Biopharmaceutics Review, FDA stated: "The pH of the formulation is critical because at pHs below 3.4 and above 3.6, degradation of vasopressin accelerates, with the degradation rate increasing as the pH deviates further from the pH 3.4-3.6 range." PTX-146 at EAGLEVAS0014353; Tr. 811:11-21 (Kirsch).

266. In the FDA Chemistry Review, FDA stated: "The pH is a critical parameter in the Pitressin formulation; in the pH range of 3.4 – 3.6, the vasopressin acid salt is relatively stable in water, and degradation accelerates at the pH that is above and below this range." PTX-309 at PAR-VASO_0238742; Tr. 811:22-812:3 (Kirsch).

267. The foregoing statements from the FDA Biopharmaceutics Review and FDA Chemistry Review taught a POSA that pH 3.4-3.6 was the pH of maximum stability for vasopressin and that vasopressin products were less stable outside of that range. Tr. 812:4-7, 826:24-827:7 (Kirsch).

268. In view of the prior art, a POSA would have expected that a vasopressin formulation would be less stable in the pH 3.7-3.9 range than in the pH 3.4-3.6 range. Tr. 812:8-22, 827:10-13, 836:8-16 (Kirsch).

269. As Dr. Kirsch testified using the demonstrative below, the FDA "comment[ed] that the optimal pH is 3.4 to 3.6 and degradation accelerates above and below that range, which is also what a person of ordinary skill would glean from original – from an original Vasostrict range and also the Bi [2000] article and the Pitressin pH." Tr. 812:8-17 (Kirsch); PDX6-8:



270. The prior art, particularly the FDA Biopharmaceutics Review, FDA Chemistry Review, and Bi 2000, taught away from the claimed pH 3.7-3.9 range. Tr. 808:6-812:22, 826:24-827:7, 833:25-834:15 (Kirsch); PTX-146 at EAGLEVAS0014353; PTX-309 at PAR-VASO_0238742; DTX-173.4.

271. There was nothing published in the prior art that would have directed a POSA towards the claimed pH 3.7-3.9 range. Tr. 808:2-5, 813:17-20 (Kirsch).

272. Defendants' contentions in DFF¶¶220-222 do not show a lack of teaching away by the FDA Biopharmaceutics and Chemistry Review. Contrary to DFF¶220, Dr. Park did not testify that the FDA Review documents "concerned only the initial pH of vasopressin formulations." *See* Tr. 422:4-20 (Park). Additionally, his testimony about the FDA Biopharmaceutics Review was focused on whether it taught away "from a formulation that was manufactured at a pH of 3.4 to 3.6 that then drifted into a pH of 3.65 for five minutes." *See* Tr. 421:23-422:20 (Park). His characterization of the above-mentioned statement in the FDA

Biopharmaceutics Review as "rather vague and uncertain" was not persuasive where it was undisputed that FDA made the statement following its review of Par's NDA, including the data therein. *See* Tr. 421:11-422:20 (Park), 810:5-811:10 (Kirsch). Additionally, contrary to DFF¶221, the FDA-approved release and stability specifications for Original Vasostrict were confidential, and therefore could not have informed a POSA about whether or not the FDA Review documents taught away from the claimed pH 3.7-3.9 range. *See* DTX-26 (designated confidential); Tr. 412:20-24 (Park).

273. Defendants' expert Dr. Park provided no opinion concerning Bi 2000's teaching away from the claimed pH 3.7-3.9 range. Defendants, however, contend that "[t]he Bi reference does not teach away from vasopressin formulations with a pH of 3.7-3.9 because it concerned the stability of vasopressin formulations with specific buffers, and in particular phosphate buffers, but different buffers can product stability profiles." DFF¶223. This is not supported by the evidence. Dr. Kirsch provided unrebutted expert testimony that Bi 2000 "conducted his studies in a different buffer and also did a study to determine whether or not the buffer had an effect and he found that the buffer did not have [an] effect on the rate, and so what he said was we're looking at a pH effect." Tr. 809:10-19 (Kirsch); *see also* DTX-173.4 (Bi 2000 concluding that "[b]uffer concentrations did not influence the degradation of [vasopressin] and therefore,

buffer ions ($H_2PO_4^-$ and HPO_4^{2-}) had no catalytic effect on [vasopressin]"). Inventor Kenney's testimony that as a factual matter he did not test every buffer, and therefore he could not conclude 3.8 is the most stable pH regardless of buffer, is not inconsistent. *See* Tr. 547:23-548:2 (Kenney). There is no evidence, nor do Defendants suggest, that Mr. Kenney is as experienced as Dr. Kirsch, or that he conducted the same extensive analysis that Dr. Kirsch did before testifying at deposition.

274. Contrary to DFF¶215, Dr. Kirsch testified that a product with pH 3.64 and a product with pH 3.65 were expected to have different properties. Tr. 850:17-21 (Kirsch); *see also* FOF253.

275. Citing the USP 2009 reference, Lithuanian patent, and "vials of Pitressin and Original Vasostrict [] sold with a pH between 3.7 and 3.9," Defendants also contend that "[v]asopressin formulations were already sold at the claimed pH of 3.7-3.9 as of the priority date; as such, the prior art did not teach away from the claimed range." DFF¶216. For the reasons expressed below (FOF276-283), Defendants' evidence did not negate the teaching away in the prior art from the claimed pH 3.7-3.9 range.

276. There is nothing in the USP 2009 reference that would have directed a POSA to the claimed pH 3.7-3.9 range. Tr. 833:20-24 (Kirsch). The USP 2009 reference disclosed that vasopressin injection products had a pH between 2.5 and

4.5. Tr. 392:4-9, 482:19-21 (Park); DTX-135.4. And, there is no stability data in the USP 2009 reference. Tr. 833:7-19 (Kirsch).

277. The pH 2.5-4.5 range disclosed in USP 2009 is also the same prior art pH range disclosed in the PPC reference that the inventors overcame during prosecution of the Asserted Patents. *See* Tr. 812:23-813:3, 776:11-21 (Kirsch); PTX-843 at PAR-VASO_0005815-5817; PTX-844 at PAR-VASO_0009720-9722; JTX-8 at PAR-VASO_0006436; JTX-9 at PAR-VASO_0010349. The pH 2.5-4.5 range entirely subsumes the claimed pH 3.7-3.9 range and the Original Vasostrict pH 3.4-3.6 range. *See* Tr. 841:5-14 (Kirsch).

278. The Lithuanian patent would not have directed a POSA to the claimed pH 3.7-3.9 range because it was directed solely to the use of animal-derived vasopressin, not synthetic vasopressin as claimed in the Asserted Patents. Tr. 831:7-832:5, 833:20-24 (Kirsch); DTX-144.3. Contrary to how Defendants characterize the evidence in DFF¶¶217-219, Dr. Kirsch provided unrebutted testimony about the numerous reasons why the pH range disclosed in the Lithuanian patent would not have informed a POSA about the pH range for a synthetic vasopressin formulation, as required by the Asserted Claims. *See* Tr. 830:21-833:24, 834:16-20, 836:19-22 (Kirsch). For example, Dr. Kirsch testified that:

- A POSA would not have reasonably expected that synthetic vasopressin could be used interchangeably with the animal-derived vasopressin disclosed in the Lithuanian patent. Tr. 836:8-22 (Kirsch).

- A POSA would not have necessarily expected the optimal formulation for an animal-derived vasopressin to be the same as the optimal formulation for a synthetic vasopressin because a POSA typically develops products based on the specific API being used. Tr. 832:6-13 (Kirsch). There are also differences between APIs that are extracted from animal sources and those which are synthetically produced. Tr. 832:13-15 (Kirsch). For example, the impurities within animal-derived vasopressin are different than the impurities within synthetic vasopressin. Tr. 892:4-895:4 (Kirsch).

- There is no stability data in the Lithuanian patent or anything that indicates that the disclosed preparation is stable. Tr. 832:20-833:6, 833:14-19 (Kirsch). And, there is no data or discussion in the Lithuanian patent that indicates that the disclosed pH range is optimal for the stability of vasopressin. Tr. 832:20-25 (Kirsch).

279. Dr. Kirsch's testimony about the lack of guidance provided by the Lithuanian patent is corroborated by the lack of evidence that anyone used the information disclosed in the Lithuanian patent for any purpose in the 18 years between its publication and the priority date of the Asserted Claims. *See* Tr. 830:21-831:6 (Kirsch).

280. A POSA would not have known anything more about the pH of Pitressin and Original Vasostrict beyond what was published. *See* Tr. 813:13-16 (Kirsch), 486:6-17 (Park). As discussed above, those published values were pH 3.6 for Pitressin and pH 3.4-3.6 for Original Vasostrict. *See, e.g.*, Tr. 807:13-808:1 (Kirsch); PTX-146 at EAGLEVAS0014352; DTX-132.5; FOF194-195. A POSA

would not have known the specific pH values of individual vials of Original Vasostrict and Pitressin products when they were on sale. *See, e.g.*, Tr. 486:6-486:17 (Park), 825:17-20, 830:15-17 (Kirsch). And, there is nothing in the prior art that would have directed a POSA to the lots of Original Vasostrict and Pitressin that Defendants selectively identified in DFF¶216 as being "sold with a pH between 3.7 and 3.9" (Original Vasostrict registration batch 310571 and lot 788436, and Pitressin lot 78495). Tr. 830:9-14, 834:11-13 (Kirsch). In fact, Original Vasostrict registration batch 310571 was never sold or in public use. Tr. 815:10-16, 822:11-17 (Kirsch); FOF205.

281. Additionally, Defendants have not presented clear and convincing evidence that Original Vasostrict lot 788436 would have had a pH of 3.7 if tested by a POSA. As explained above, lot 788436 was measured with pH 3.7 approximately 9 months before it was sold, and there was no pH data for lot 788436 when it was on sale. Tr. 822:22-823:9, 823:17-20 (Kirsch); FOF221-222, 230-231.

282. All pH measurements taken after the time of manufacture for commercial lots of Original Vasostrict were reported at pH 3.6 or lower. Tr. 414:9-14 (Park), 824:9-20, 857:20-858:2 (Kirsch); DTX-360.11, 19, 23, 26, 28. Thus, the evidence indicates that had a POSA tested a commercial lot of Original

Vasostrict at random, its pH value would almost certainly have been below the claimed pH 3.7-3.9 range. *See id.*

283. There is also no evidence that a POSA could have measured the pH of Pitressin lot 78495 as of the priority date of the Asserted Claims. Defendants state that "[a] POSA would have been able to test the properties of a vasopressin product available on the market" (DFF¶74), but lot 78495 was not available on the market as of the February 7, 2017 priority date. Rather, the lot expired seven years earlier, in February 2010. Eagle PTO Ex. 1, ¶ 59.

284. Additionally, Pitressin lot 78495 did not concurrently meet the pH and impurity limitations of the Asserted Claims. Tr. 825:6-16, 825:21-826:1 (Kirsch).

285. There was also no publicly available information about either the impurities within Pitressin or the rate of impurity formation in Pitressin. Tr. 825:2-5 (Kirsch).

2. Lack of Motivation

286. Defendants contend that "[a] POSA would have looked to Original Vasostrict and its properties, including its labeled pH range of 3.4 to 3.6, in formulating a vasopressin product as of the priority date." DFF¶75. But there is no evidence establishing that a POSA would have been motivated to formulate an improved (in particular, a more stable) vasopressin product as of the priority date. *See, e.g.*, Tr. 395:10-16 (Park), 826:8-827:7, 829:13-22, 833:25:834:15 (Kirsch).

287. It is undisputed that a POSA would not have been motivated to improve vasopressin stability or to lower impurities to any specific claimed level. Tr. 833:25:834:10, 826:24-827:7 (Kirsch).

288. Of the more than 50 lots of Original Vasostrict that were sold before the priority date of the Asserted Patents, Defendants' expert Dr. Park addressed only two lots—lot 788435 and lot 788436. Tr. 396:24-397:4, 410:21-25, 418:11-16 (Park), 823:15-16, 830:2-8 (Kirsch); DTX-86; DTX-1362. A POSA would not have known the specific pH or impurities of either lot. Tr. 830:15-20 (Kirsch); *see also* Tr. 486:6-17 (Park). And, there was nothing in the prior art that would have directed a POSA to those particular lots among all the lots Par sold. Tr. 830:9-14, 834:11-13 (Kirsch).

H. No Reasonable Expectation of Success

289. As Eagle's counsel acknowledged, Dr. Park did not testify that there would have been a reasonable expectation of success in the prior art. *See, e.g.*, Tr. 834:21-835:2 (Kirsch), 835:10-19 (Eagle's counsel). Thus, it is undisputed that a POSA would not have reasonably expected to succeed in achieving the claimed inventions. *See id.*; Tr. 826:8-827:13, 836:8-22.

290. There was not a reasonable expectation that the claimed pH 3.7-3.9 values would have an improvement in stability. Tr. 812:8-22, 827:10-13, 836:8-16 (Kirsch); FOF260-269.

291. A POSA would not have reasonably expected to achieve the specific impurity levels that are recited in the Asserted Claims. Tr. 835:3-7, 836:1-18 (Kirsch).

292. Defendants contend that "[a] POSA would have expected a vasopressin formulation based on Original Vasostrict to maintain low impurities under refrigeration." DFF¶162 (citing Kirsch Tr. 849:20-850:1). In the cited testimony, however, Dr. Kirsch did not testify that Original Vasostrict would "maintain low impurities" under refrigeration; rather he agreed that refrigeration would be expected to slow the rate of degradation. Tr. 849:20-850:1. As Dr. Kirsch explained, the impurities and impurity levels within vasopressin products were unknown in the prior art. Tr. 206:14-18, 807:10-12, 830:18-20, 836:1-18 (Kirsch). Thus, a POSA would not have known the amount of impurities within Original Vasostrict. *See id.*

I. A POSA Would Not "Have Achieved the Claimed Invention by Making Original Vasostrict as a Matter of Course"

293. Defendants contend that "[a] POSA adopting the Original Vasostrict formulation as of the Asserted Patent priority date would not have been concerned about pH drifting within the shelf life specification of 2.5-4.5, including into the claimed range of 3.7-3.9." DFF¶160 (citing Park Tr. 421:23-422:20; PTX-146 at EAGLEVAS0014353; PTX-309 at PAR-VASO_0238742; Kirsch Tr. 813:9-12). This contention is not supported by the testimony and exhibits cited by Defendants.

It is also inconsistent with the evidence. A POSA would not have known the shelf life specification of Original Vasostrict because it was confidential. *See* DTX-26.26 (designated confidential); Tr. 412:20-24 (Park). In fact, a POSA would not have known anything about the pH of Original Vasostrict beyond its published pH 3.4-3.6 range. *See* 813:13-16, 807:13-21 (Kirsch), 482:15-18, 486:6-17 (Park), 613:19-24 (Chyall); DTX-132.5; *see also* DFF¶¶38, 88. Thus, a POSA would not have expected the pH of Original Vasostrict to "drift" into the claimed pH 3.7-3.9 range. *See id.*

294. Defendants also contend that Original Vasostrict "was permitted to drift" and "drifted outside of the pH range of 3.4 to 3.6 at release and over shelf life." DFF¶¶161, 163 (citing data regarding Original Vasostrict registration batch 310571 (DTX-27.34, 36) and lot 788436 (DTX-1314.1)). There is no evidence in the record that suggests that the pH of Original Vasostrict drifts in the manner Defendants imply. Because Defendants identify only one value for Original Vasostrict lot 788436, there is no evidence that it "drifted." *See* Tr. 418:5-8 (Park); DTX-1314.1. As for registration batch 310571, there is no evidence that the single pH 3.8 measurement at 18 months was ever verified. Tr. 815:20-816:11 (Kirsch). And, there was no evidence of any Original Vasostrict product that had a pH of 3.7, 3.8, or 3.9 when it was on sale or in public use. *See, e.g.*, Tr. 823:21-824:5, 824:9-20 (Kirsch); FOF205, 231, 232, 242. Moreover, the evidence indicates that

an Original Vasostrict product would almost certainly be measured with a pH of 3.6 or lower throughout its shelf life. *See* FOF209, 223, 232, 242, 282.

295. The evidence also shows that no Original Vasostrict product concurrently met the pH and impurity limitations of the Asserted Claims. *See* FOF201-203, 220, 229, 241, 244.

296. Thus, contrary to DFF¶165, there is no evidence that "[a] POSA making a formulation based on the Original Vasostrict prior art who allowed the formulation to drift within its shelf life pH specification to the claimed pH range would have achieved the claimed inventions as a matter of course." FOF293-295.

J. Objective Evidence of Non-Obviousness: Criticality and Unexpected Results of the Claimed pH 3.7-3.9 Range

297. The evidence at trial, discussed in more detail below, established that the claimed pH 3.7-3.9 range was critical to vasopressin product stability. *See, e.g.*, Tr. 767:5-10, 854:23-25 (Kirsch); *see generally* Tr. 766:17-790:1, 795:23-805:15, 885:3-887:9, 888:5-889:22 (Kirsch).

298. The evidence at trial, discussed in more detail below, established that the claimed pH 3.7-3.9 range achieved unexpected results. *See, e.g.*, DTDX-10 (Sanghvi 2020 Tr.) 115:25-116:1, 116:4-5, 116:10-16; Tr. 812:8-22, 827:10-13, 836:8-16 (Kirsch); *see generally* Tr. 766:17-790:1, 795:23-805:15, 885:3-887:9, 888:5-889:22 (Kirsch).

299. During prosecution, the inventors presented information supporting the criticality of the claimed pH 3.7-3.9 range. Tr. 767:11-16 (Kirsch). That information included declarations by inventor Vandse and inventor Kannan containing data and results from their pH studies, which were conducted at 25 and 40 degrees Celsius for four weeks (one month) over a pH range of 2.5 to 4.5. Tr. 768:9-770:20 (Kirsch); DTX-7.1883-1896 (Vandse Jan. 2016 declaration); DTX-7.2159-2169 (Kannan Mar. 2016 declaration); DTX-10.2352-2372 (Kannan May 2017 declaration); *see also* Tr. 616:13-20 (Chyall).

300. The pH study data from the inventor declarations are presented in the Asserted Patents in Examples 9-11 and Figures 11-18. Tr. 775:16-776:10 (Kirsch); JTX-2; JTX-3; *see also* Tr. 563:8-14, 567:23-568:6 (Chyall); DFF¶190.

301. The inventors identified pH 3.7-3.9 as the region of optimal stability. Tr. 770:8-20 (Kirsch). During prosecution of the Asserted Patents, Par told the Examiner that "[t]he present specification establishes the criticality of pH 3.7-3.9 in limiting the amount of impurities in a vasopressin formulation" and reproduced one of the figures from the Vandse declaration that showed the pH minimum region for total impurity data at 40°C. Tr. 775:16-776:25 (Kirsch); PTX-843 at PAR-VASO_0005816-5817; PTX-844 at PAR-VASO_0009721-9722.

302. Contrary to DFF¶191, the pH studies demonstrate criticality of the claimed pH 3.7-3.9 range. Tr. 805:5-15, 769:20-770:20, 786:9-787:9 (Kirsch).

303. And, contrary to DFF¶¶196-199, the pH studies demonstrate criticality of the full scope of the claimed pH 3.7-3.9 range, not limited to the specific buffer or formulations tested. Tr. 724:14-726:22 (Kannan), 805:5-15 (Kirsch). The only difference between the formulations tested in the pH studies was the pH—each solution contained 20 units/mL vasopressin, adjusted to a certain pH with 10 mM acetate buffer, which were then filled into 10 cc vials. *See, e.g.*, JTX-2 at 97:45-49, 98:8-12. Because "pH was the only variable that was not normalized," meaning that "the pH was not the constant between formulations," inventor Kannan concluded in his declarations that "the differences in the assay (% label claim; vasopressin remaining) and % total impurities results for each formulation were ***attributable to changes in pH***." DTX-1073 ¶ 32 (emphasis added); Tr. 724:14-727:16 (Kannan); PTX-330 ¶ 16. And, as Dr. Kirsch testified: "The studies that were done to look at pH were done in acetate buffer. The inventors also reported on the effect of acetate buffer, if you will, on degradation. They found that it had no effect on degradation. . . . ***So the effects that they are looking at are pH effects. They demonstrate the pH criticality***." Tr. 805:5-15 (Kirsch) (emphasis added). With respect to inventor Kenney's testimony Defendants cite in DFF¶¶196, 197, 199, there is no evidence, nor do Defendants suggest, that Mr. Kenney is as experienced as Dr. Kirsch, or that he conducted the same extensive analysis that Dr. Kirsch did before testifying at deposition.

304. The Examiner concluded that the claimed pH 3.7-3.9 range was critical. JTX-8 at PAR-VASO_0006436; JTX-9 at PAR-VASO_0010349.

305. Dr. Kirsch also concluded that the claimed pH range of 3.7-3.9 was critical to vasopressin product stability. *See, e.g.*, Tr. 767:5-10, 854:23-25 (Kirsch).

306. Dr. Kirsch performed an independent statistical analysis of the 40°C data from the Vandse declaration to confirm the inventors' conclusions regarding the criticality of pH 3.7-3.9. Tr. 777:1-787:9 (Kirsch). Using Par's data for its analytical method for measuring impurities to make a conservative estimate of standard deviation, Dr. Kirsch calculated whether the difference in the total impurity appearance rate (that is, normalized impurity data) was statistically significant between the claimed pH 3.7-3.9 values and the other values within the pH 2.5-4.5 range. Tr. 778:1-786:18 (Kirsch); DTX-1143 at PAR-VASO_0031690.

307. The 40°C data that Dr. Kirsch used for his statistical analysis provided enough degradation to allow distinctions to be made between the effects of pH. Tr. 771:3-772:9, 849:6-15 (Kirsch); DTX-7. 1888. In contrast, there was not enough degradation in the 25°C experiment to understand the effects of pH on the degradation of vasopressin. Tr. 771:9-772:9, 804:17-25 (Kirsch). During his testimony, Dr. Chyall focused primarily on the 25°C data from the inventor declarations. Tr. 616:6-9 (Chyall), 804:17-25 (Kirsch).

308. Contrary to DFF¶201 (citing Chyall testimony), Dr. Chyall did not provide a principled explanation for his conclusion. Rather, he failed to differentiate the more relevant 40°C data from the less relevant 25°C data, and then eyeballed the graphs without doing any data analysis and identified "values that [he] considered to be comparable." *See generally* Tr. 576:17-591:7 (quote at 585:22-586:3). By contrast, Dr. Kirsch performed a methodical, statistical analysis of the most relevant data. *See, e.g.*, Tr. 777:1-787:9 (Kirsch).

309. Dr. Chyall testified that he has only "some limited experience with peptide stability." Tr. 612:20-613:1 (Chyall). He also acknowledged that "Dr. Kirsch has a lot more experience with peptides" than he does. Tr. 620:13-16 (Chyall). Dr. Park, whom Dr. Chyall also admitted "has a lot more experience with peptides" than he does, did not testify about the inventors' pH experiments. Tr. 620:17-21 (Chyall).

310. Based on Dr. Kirsch's statistical analysis, he concluded that: (1) there were statistically significant differences between the claimed pH 3.7, 3.8, and 3.9 values and each value between 2.5 and 3.6 and most values between 4.0 and 4.5; (2) the claimed values represented the values of minimum instability or maximum stability in terms of the total impurity appearance rate; (3) there is greater stability for vasopressin preparations within the claimed 3.7-3.9 range than outside of it; and (4) the data in the Vandse declaration justified the inventor's conclusion. Tr.

783:19-787:9 (Kirsch). Dr. Kirsch used the following demonstrative to show the results of his statistical analysis:

pH	Change in Impurities 40°C	Mean difference compared to pH 3.8 value	Statistically Significant (mean difference > 0.28%)		
			Compared to 3.7	Compared to 3.8	Compared to 3.9
2.5	16.93 ± 0.14	16.05	Yes	Yes	Yes
2.6	13.36 ± 0.14	12.48	Yes	Yes	Yes
2.7	11.2 ± 0.14	10.32	Yes	Yes	Yes
2.8	8.98 ± 0.14	8.10	Yes	Yes	Yes
2.9	7.83 ± 0.14	6.95	Yes	Yes	Yes
3.0	6.20 ± 0.14	5.32	Yes	Yes	Yes
3.1	4.33 ± 0.14	3.45	Yes	Yes	Yes
3.2	3.40 ± 0.14	2.52	Yes	Yes	Yes
3.3	2.60 ± 0.14	1.72	Yes	Yes	Yes
3.4	2.10 ± 0.14	1.22	Yes	Yes	Yes
3.5	1.68 ± 0.14	0.80	Yes	Yes	Yes
3.6	1.64 ± 0.14	0.76	Yes	Yes	Yes
3.7	1.09 ± 0.14	0.21	–	No	Yes
3.8	0.88 ± 0.14	0	No	–	No
3.9	0.70 ± 0.14	-0.18	No	No	–
4.0	0.90 ± 0.14	0.02	No	No	No
4.1	1.22 ± 0.14	0.34	No	Yes	Yes
4.2	1.82 ± 0.14	0.94	Yes	Yes	Yes
4.3	2.54 ± 0.14	1.66	Yes	Yes	Yes
4.4	3.06 ± 0.14	2.18	Yes	Yes	Yes
4.5	5.38 ± 0.14	4.50	Yes	Yes	Yes

Claimed pH range

"Normalized" impurities

PDX6-23.

311. Defendants contend that Dr. Kirsch's analysis showed that pH 4.0 "did not produce a statistically significant difference in impurities compared to the claimed range." DFF¶206. Dr. Kirsch testified, however, that the criticality of the claimed pH 3.7-3.9 range over pH 4.0 is confirmed once the loss of vasopressin data are additionally considered. Tr. 885:3-886:15 (Kirsch). As Dr. Kirsch testified: "And if one looks at the loss of vasopressin and then the data at pH four [4.0] is significantly less, there's significantly less stability than what one can see in the claimed range." Tr. 885:21-24 (Kirsch).

312. Dr. Kirsch's statistical analysis demonstrates the criticality of the claimed pH 3.7-3.9 range over the prior art pH 2.5-4.5 range and over the prior art pH 3.4-3.6 range. *See, e.g.*, Tr. 777:1-4, 783:19-787:9, 854:9-855:6 (Kirsch).

313. In DFF¶202, Defendants state that "[a]ny difference in the stability of vasopressin formulations demonstrated by the stability studies is at most a difference in degree, not kind[.]" Dr. Kirsch's statistical analysis, however, shows otherwise. For example, compared with the pH 3.8 formulation, the pH 3.6 formulation showed an 86% increase in the total impurity appearance rate over only four weeks at 40°C (1.64% versus 0.88%). Tr. 783:19-784:17 (Kirsch). Moreover, Dr. Kirsch explained that in the field of peptide stability, the overall rate of impurity formation is the sum of multiple parallel degradation pathways, each with their own pH dependence. Tr. 803:8-19 (Kirsch). Thus, a POSA would not have expected a sharp change in stability between abutting pHs, particularly here, where a POSA would not have expected the claimed pH 3.7-3.9 range to provide any improvement in stability. *See id.*; FOF260-269, 290, 330.

314. Contrary to DFF¶¶204-206, Dr. Kirsch explained why his determination of statistically significant differences showed the criticality of the claimed pH 3.7-3.9 range. Tr. 854:9-855:20 (Kirsch). As Dr. Kirsch testified:

> Q. Okay. Now, area you equating statistical significance with criticality?

> A. I'm using statistical difference to make, to determine whether or not there is a difference. So, you know, if the difference is statistically significant, then it could well be critical.

Tr. 854:9-14 (Kirsch). Dr. Kirsch then showed why in this instance, the statistically significant results from the pH studies described in the inventor declarations establish a critical difference by showing that, in the real world, the pH difference has a meaningful effects on stability and shelf life. *See* FOF318-330.

315. Contrary to Defendants' suggestion in DFF¶208, Dr. Kirsch has the appropriate experience in statistics to offer the statistical opinions that he presented at trial. Dr. Kirsch testified about that experience, including that performing statistical analyses to evaluate peptides and stability to make formulations is "a key part of [his] – [his] activities in studying the stability and degradation kinetics of peptides, which [he's] been doing over [his] professional career . . . ." Tr. 777:5-25 (Kirsch).

316. Dr. Kirsch also showed that Amneal's expert Dr. Marais performed his own statistical analysis of the data from the Vandse declaration and from a different set of experiments to compare the claimed pH 3.7-3.9 range to pH 3.6, and found a statistically significant difference between them. Tr. 787:10-789:20 (Kirsch).

317. In DFF¶210, Defendants inappropriately cite demonstrative PDX6-25 as evidence to show other aspects of Dr. Marais's analysis. Defendants chose not to call Dr. Marais (Tr. 794:4-13), and therefore he neither explained his methodology, nor did Par have an opportunity to cross-examine him on the aspects of his opinion that Defendants now seek to introduce. Dr. Kirsch, who actually testified at trial and explained his analysis in great detail, showed that there was a statistically significant difference in the rate of change in impurities between the claimed pH 3.7-3.9 range and pH 3.6. *Compare* Tr. 777:1-787:9 (Kirsch) *with* DFF¶210. Regardless of the other aspects of his analysis, Dr. Marais—the statistics expert Defendants chose not to call—also found a statistically significant difference between the claimed pH 3.7-3.9 range and pH 3.6, and that finding supports the criticality of the claimed range. *See* Tr. 788:2-789:15 (Kirsch).

318. For the reasons expressed below (FOF319-330), there are meaningful improvements in stability when comparing the claimed vasopressin formulations within the claimed pH 3.7-3.9 range with vasopressin formulations outside of the claimed pH 3.7-3.9 range, and specifically in the pH 3.4-3.6 range. Tr. 796:5-803:7 (Kirsch). These meaningful improvements further support the criticality of the claimed pH 3.7-3.9 range over the prior art pH 3.4-3.6 range. *Id.*

319. Reformulated Vasostrict embodies the claimed invention of the Asserted Claims. Tr. 766:25-767:4, 837:17-22, 863:13-864:2 (Kirsch); *see also* Tr.

839:4-840:9 (Kirsch); DFF¶64 ("The claims of the '209 and '785 Patents cover Reformulated Vasostrict . . . .").

320. Dr. Kirsch compared the stability data across 12 months at room temperature for Reformulated Vasostrict registration batches at pH 3.7-3.9 as compared with Original Vasostrict registration batches at pH 3.4-3.6 (with one measurement being pH 3.2). Tr. 796:5-798:16, 863:13-864:12 (Kirsch); DTX-53.28-33; PTX-411 at PAR-VASO_0070232-235, 240-243, 248-251. Dr. Kirsch testified that across the 12-month room temperature shelf life, Reformulated Vasostrict had a 3.5% average increase in total impurities, whereas Original Vasostrict had a 4.5% average increase in total impurities—a 22% reduction for Reformulated Vasostrict. Tr. 797:12-799:19, 864:13-23 (Kirsch); DFF¶174.

321. In DFF¶177, Defendants state that the difference in stability between Reformulated and Original Vasostrict "is at most a difference in degree, not kind" because there is only a 1-2% difference in impurities. Defendants, however, ignore that the comparison shows a 22% reduction in the rate of formation of total impurities. FOF320. A POSA would consider a 22% reduction in the rate of formation of total impurities across 12 months at room temperature to be a meaningful improvement in stability and one with significance. Tr. 798:17-799:1 (Kirsch).

322. Dr. Kirsch testified that he was using the comparison between Reformulated and Original Vasostrict "as support for [his] evidence that there is a ***critical*** difference," not a "***clinical*** difference," as Defendants contend in DFF¶173. *See* Tr. 863:13-864:12 (Kirsch) (emphasis added); *see also* Tr. 799:13-19.

323. The inventors testified that Par's data showed a four-month enhancement in the estimated room temperature shelf life for Reformulated Vasostrict compared with Original Vasostrict—19 months versus 15 months—which would support a marketed 18-month room temperature shelf life for Reformulated Vasostrict. DTDX-2 (Kannan 2019 Tr.) 235:18-22, 235:24-236:5, 297:9-298:5, 298:8-298:13; DTDX-3 (Kenney 2019 Tr.) 87:15-88:5; DTDX-4 (Kenney 2020 Tr.) 154:14-15, 154:17-25, 217:3-17, 217:19-21, 219:19-24, 220:20-221:7; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12; *see also* Tr. 888:5-17 (Kirsch). For example, inventor Kenney testified:

> **Q.** Did you and the other coinventors of the '785 patent later collect more data for the stability of the reformulated Vasostrict product relative to the original Vasostrict product?
>
> **A.** Yes.
>
> **Q.** And what did the data show with respect to the relative assay over shelf life?
>
> **A.** So the estimate shelf life of the original Vasostrict was around 15 months. The reformulated Vasostrict with the 3.8 pH acetate buffer, the shelf life was increased to around 19 months.

> **Q.** And similarly what did the data show with respect to the relative amount of impurities over the shelf life?
>
> **A.** So I don't remember those numbers, but the amount of impurities was decreased dramatically over the estimated shelf life.
>
> ***
>
> **Q.** Just one more question, Mr. Kenney. Even though the labels are the same with respect to storage conditions for the original formulation of Vasostrict and the reformulated product, does Par have data to support a longer shelf life out of refrigeration for the reformulated product?
>
> **A.** Yeah, so our data indicates an estimated shelf life with 95 percent confidence interval of 19 months, which means that it is possible to have this product on the market with an 18-month room temperature shelf life on the label.

DDTX-4 (Kenney 2020 Tr.) at 217:3-17, 217:19-21, 220:20-221:7. Contrary to DFF¶185, the data corroborating the estimated room temperature shelf lives for Reformulated and Original Vasostrict are in the record. *Compare* PTX-252 at PAR-VASO_0030582 *with* DTX-53.19.

324. A POSA would consider a four-month increase in room temperature shelf life for Reformulated Vasostrict to be a meaningful improvement (Tr. 799:20-800:4, 888:5-17 (Kirsch)), contrary to Defendants' contention in DFF¶177 that the difference in stability "is at most a difference in degree, not kind."

325. Contrary to Defendants' suggestion otherwise (DFF¶¶179, 185), the fact that Reformulated Vasostrict and Original Vasostrict have the same approved shelf-life and impurity specifications is not relevant because the data shows the

superiority of Reformulated Vasostrict. *See* FOF323-324. And, as Dr. Kirsch testified, the decisions about shelf life dating and impurity specifications are "outside the scientific assessment of criticality" and "based on other decisions other than simply the rate of change in those samples." Tr. 800:5-19 (Kirsch).

326. Dr. Kirsch also compared the stability data across 12 months at room temperature for Reformulated Vasostrict registration batches at pH 3.7-3.9 as compared with Eagle registration batches SVA002 and SVA003 at pH 3.4-3.6. Tr. 800:20-801:11, 801:22-802:2, 865:4-11 (Kirsch); DTX-125.2, 4; DTX-128.2, 4; PTX-411 at PAR-VASO_0070232-235, 240-243, 248-251. Dr. Kirsch testified that across the 12-month room temperature shelf life, Reformulated Vasostrict had a 3.5% average increase in total impurities, whereas Eagle registration batches SVA002 and SVA003 had a 5.5% average increase in total impurities—a 36% reduction for Reformulated Vasostrict. Tr. 800:20-801:11, 865:15-21 (Kirsch); DFF¶174.

327. In DFF¶177, Defendants state that the difference in stability between Reformulated and Eagle registration batches SVA002 and SVA003 "is at most a difference in degree, not kind" because there is only a 1-2% difference in impurities. Defendants, however, ignore that the comparison shows a 36% reduction in the rate of formation of total impurities. FOF326. A 36% reduction in

the rate of formation of total impurities across 12 months at room temperature is a meaningful change. Tr. 801:12-15 (Kirsch).

328. Dr. Kirsch also testified that he analyzed "all of the available room temperature 12-month data" for Reformulated Vasostrict, Original Vasostrict, and Eagle's ANDA product, and "found statistically significant differences between both the rate of vasopressin lost and the appearance of impurities." Tr. 802:22-803:7, 886:16-887:9 (Kirsch).

329. The foregoing stability advantages for vasopressin formulations within the claimed pH 3.7-3.9 range have real-world benefits. For example, the room temperature shelf life for Reformulated Vasostrict could be extended from 12 to 18 months. FOF163, 323; DTX-151.4 (12 month room temperature shelf life). And, because drug potency is lost as the drug degrades, slowing degradation leads to a more efficacious drug product. Tr. 202:8-203:7 (Kirsch). Additionally, as inventor Vandse testified, "[l]ess impurities means it is less side effect or safer for the patient." DTDX-7 (Vandse 2019 Tr.) 251:22-252:6.

330. In view of the prior art teachings that a vasopressin formulation would be less stable in the pH 3.7-3.9 range, the stability advantages achieved by the claimed pH 3.7-3.9 range were unexpected. *See, e.g.*, DTDX-10 (Sanghvi 2020 Tr.) 115:25-116:1, 116:4-5, 116:10-16; Tr. 812:8-22, 827:10-13, 836:8-16 (Kirsch); FOF260-269.

331. Citing Dr. Chyall's testimony, Defendants contend that "[b]ecause Reformulated Vasostrict has a different formulation than Original Vasostrict and Eagle's ANDA Product, 'it's not possible to attribute any difference in performance [to] just pH, because there are other variables in these products." DFF¶¶183-184; *see also* DFF¶186. However, Dr. Kirsch, whom Dr. Chyall acknowledged "has a lot more experience with peptides" than he (Tr. 620:13-16), testified:

> I've looked at the – their compositions of those – of these products and, you know, the differences are, in my view are not – are not significant relative to the differences in pH.
>
> The pH effect is the predominant effect. I mean, if you look, for instance, they both contain acetate and the only real difference in composition is the chlorobutanol and it seems unlikely to me that Eagle would use a preservative that it could adversely affect the stability. That doesn't seem to be reasonable either.

Tr. 802:12-21. Moreover, with respect to inventor Kenney's testimony Defendants cite in DFF¶186 (Tr. 551:12-552:17), he was not addressing any "stability difference between Reformulated Vasostrict and Original Vasostrict." Moreover, there is no evidence, nor do Defendants suggest, that Mr. Kenney is as experienced as Dr. Kirsch, or that he conducted the same extensive analysis that Dr. Kirsch did before testifying at deposition.

332. Defendants contend that "Dr. Kirsch's comparisons do not evaluate criticality of the claimed pH over the full scope of the claims because

Reformulated Vasostrict is formulated to have an initial pH at or near 3.8, not 3.7 or 3.9." DFF¶181. That is incorrect. As Dr. Kirsch testified and the stability data for Reformulated Vasostrict makes clear, the pH of the Reformulated Vasostrict registration batches spanned the full pH 3.7-3.9 range over the course of the 12 months at room temperature. Tr. 797:6-11, 798:8-12, 801:6-9, 863:19-864:2, 865:4-8 (Kirsch); PTX-411 at PAR-VASO_0070232-235, 240-243, 248-251.

333. Contrary to DFF¶187, the release and shelf life specifications for Reformulated Vasostrict are not relevant to the criticality of the claimed pH 3.7-3.9 range. Tr. 803:23-804:16, 844:14-23 (Kirsch). Regardless of those specifications, Reformulated Vasostrict "never trends outside" the claimed 3.7-3.9 range for its shelf life. DTDX-3 (Kenney 2019 Tr.) 70:18-71:5; Tr. 803:23-804:16 (Kirsch). Moreover, Dr. Chyall did not show any pH data for Reformulated Vasostrict outside of the 3.7-3.9 range. Tr. 803:23-804:16 (Kirsch).

334. Defendants contended that the "pH stability studies . . . did not evaluate the stability of formulations that start with a pH outside of the claimed range of 3.7-3.9, that then drift into the claimed pH range during the shelf life." DFF¶195; *see also* DFF¶¶193, 194. They make the same contention for Dr. Kirsch's Reformulated Vasostrict comparisons. DFF¶182. However, Dr. Kirsch testified that there would be a stability benefit in going into the claimed pH 3.7-3.9 range, even for five minutes or less, because the rate of degradation will slow up:

Q. Now, is it sufficient to go into the claim range for one minute?

A. Well, yes. I mean, you know, the stability is due to a – the effect of rate or the effect of pH on rate, so if you're at pH seven [sic, 3.7], then you have that effect.

***

Q. And you would agree that from a stability perspective or impurity perspective, you don't expect any benefit to occur by being in the claimed range for five minutes?

A. Well, the benefit is only that the rate of degradation would be responsive to the pH at that point in time.

Q. But if it only spends five minutes in the claimed range, you would agree, you're not going to see an actual benefit in stability because you need to spend time there to have a benefit in terms of stability; correct?

A. Well, the – ***the benefit that you see is because the pH is controlling the rate and if the pH gets into a certain range, then the rate will slow up. So, I mean the benefit is in terms of the stability of the product.*** I'm not, I'm not sure what you are getting to.

Tr. 301:2-6, 301:13-302:1 (Kirsch) (emphasis added).

335. Contrary to DFF¶167, inventor Kenney testified about the "critical difference in stability of vasopressin formulations that have the pH of 3.6 compared to pH of 3.8." For example:

Q. Can you quantity how much better 3.8 pH is compared to a 3.6 pH?

A. So one thing that we can quantify is our current formulation versus the previous Vasostrict, which the previous Vasostrict had an estimated shelf life of 15 months. And then with our formulation work, we were able to improve the estimated shelf life to 19 months.

Q. And is that out of refrigeration, in refrigeration, or what?

A. That's room temperature stability.

DTDX-4 (Kenney 2020 Tr.) 154:14-15, 154:17-25. Kenney and the other inventors provided additional testimony about the advantages shown by Reformulated Vasostrict as compared to Original Vasostrict. *See, e.g.*, DTDX-3 (Kenney 2019 Tr.) 87:15-88:5, 89:8-13, 89:16-18, 89:20-21; DTDX-4 (Kenney 2020 Tr.) 217:3-17, 217:19-21, 219:19-24, 220:20-221:7; DTDX-2 (Kannan 2019 Tr.) 235:18-22, 235:24-236:5, 297:9-298:5, 298:8-298:13; DTDX-7 (Vandse 2019 Tr.) 152:20-153:15, 251:22-252:6; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12.

336. Contrary to DFF¶168 and ¶203, Dr. Kirsch testified that under high enough temperatures, "you would see a difference" in stability between a sample at pH 3.65 compared with one at pH 3.64 that spent five minutes at pH 3.65. Tr. 852:17-853:3 (Kirsch); *see also* FOF253.

337. In DFF¶211, Defendants contend that Par alleged "that the stability studies show the criticality of three distinct pH ranges or values in different patent prosecutions." The same Examiner (Christina Bradley) prosecuted each of the '209, '785, '239, '478, and '526 patents identified by Defendants, and therefore would have been aware of any allegations made by Par about criticality in those prosecutions. *See* Eagle PTO Ex. 1 ¶ 33; Amneal PTO Ex. 1 ¶ 35; DTX-7.348; JTX-1 at cover.

VII. INEQUITABLE CONDUCT THEORY I: DR. KANNAN'S INVENTORSHIP DECLARATION

A. Dr. Kannan's November 2015 Inventorship Declaration Was Not False

1. Kannan's Work on Refrigerated Storage of Vasopressin

338. Dr. Vinayagam Kannan worked on several projects concerning the research and development of Par's original and reformulated Vasostrict products. The first involved refrigerated storage of diluted vasopressin preparations. Tr. 712:5-12, 712:19-713:15 (Kannan). His work involved troubleshooting the dilution of vasopressin in 5% dextrose, which had been discouraged because of perceived incompatibility and declines in potency. Tr. 712:19-713:15 (Kannan).

339. Later, Kannan worked on a project involving refrigerated storage of Vasostrict vials. Tr. 713:16-714:9 (Kannan). The originally-approved shelf life for Vasostrict was 12 months at room temperature, and he worked with others, including Matthew Kenney, to evaluate data, perform analyses, and make recommendations to management to obtain a 24-month refrigerated shelf life for Vasostrict. *Id.* Par successfully obtained a 24-month shelf life under refrigerated storage conditions. Tr. 714:5-9 (Kannan).

340. Par prosecuted patent applications directed to the discoveries Kannan made regarding the refrigerated storage of Vasostrict, including U.S. Application No. 14/717,877, which issued as U.S. Patent No. 9,744,239.[4] *E.g.*, DTX-605.

2. The Inventorship Declaration

341. During prosecution of the '239 patent, Examiner Christina Bradley issued an Office Action, dated October 21, 2015, rejecting the then-pending claims in view of the April 2014 Vasostrict Label. DTX-10.1873-1877.

342. The independent claim pending at the time recited the following:

> 16. (New) A method of increasing blood pressure in a human in need thereof, the method comprising:
>
> a) providing a pharmaceutical composition for intravenous administration comprising, in a unit dosage form: i) from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof; ii) chlorobutanol; iii) acetic acid; and iv) water, wherein the unit dosage form has a pH of 3.4 to 3.6;
>
> b) storing the unit dosage form at 2-8 °C; and
>
> c) administering the unit dosage form to the human;
>
> wherein:
>
> the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute; and
>
> the human is hypotensive.

DTX-10.0612; Tr. 716:4-717:9 (Kannan).

[4] The claims were amended during prosecution, and Par ultimately removed the refrigerated storage limitations, such that the as-issued claims of the '239 patent were directed to a different invention. *See* DTX-605.0033-34.

The principal point of novelty being argued by Par at that time was the limitation reciting storage at 2-8ºC (refrigerated conditions). *See* DTX-10.0616-618.

343. Dependent claims 17, 18, and 19 added that the unit dosage form further comprised specified levels of different SEQ ID NOs. after storage for 4 weeks at 2-8ºC. DTX-10.0612-0613; Tr. 442:14-20 (Park).

344. Examiner Bradley relied on the April 2014 Vasostrict Label to reject the pending claims, including claims 16-19, as anticipated or, in the alternative, obvious:

> The FDA label teaches a method to increase blood pressure in adults with vasodilatory shock (e.g. post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines (section 1) comprising:
>
> a) providing a pharmaceutical composition containing vasopressin for intravenous administration in a unit dosage form that contains vasopressin at 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and water for Injection, and a pH adjusted with acetic acid to pH 3.4 – 3.6. (section 11);
>
> diluting the vasopressin unit dosage form with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration (section 2.1);
>
> b) refrigerating the diluted solution for up to 24 hours (section 2.1); and
>
> c) administering the vasopressin by intravenous route at a dose of 0.03 to 0.1 units/minute for post-cardiotomy shock (section 2.2) or 0.01 to 0.07 units/minute for septic shock (section 2.2).

DTX-10.1874.

345. Examiner Bradley stated that the 0.01% SEQ ID after 4 weeks storage at 2-8ºC limitations of claims 17-19 were "an inherent feature of the prior art

formulation," but cited no evidence and provided no explanation as to the basis for that conclusion. DTX-10.1875. No expert or other evidence was ever presented on this issue during prosecution. *See generally* DTX-10. As detailed above, both sides' experts disagree, each concluding that impurity levels and other properties can be affected by, among other things, the manufacturing process and API used to make the product. *See* FOF151, 246-247; Tr. 202:7-203:7 (Kirsch), 476:6-478:23 (Park).

346. In response to the Examiner's rejection, prosecuting attorney Craig Kenesky submitted a draft declaration to the Examiner. DTX-10.1955. It stated in paragraph 6 that Kannan and Kenney "invented" the "subject matter" of the then-pending patent claims. DTX-10.1957.

347. The declaration further stated in paragraph 7:

> 7. The Label discloses part of the subject matter of the claims, including a method of increasing blood pressure in a hypotensive human. The Label recites that, "[v]asostrict is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive . . . ." *Label*, page 1 (parentheticals omitted). The Label further recites a pharmaceutical composition for intravenous administration having 20 units of vasopressin per mL . . . ." *Label*, page 3. The Label further recites that the vasopressin formulation comprises "chlorobutanol [and] Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6." *Label*, page 6. The Label recites the infusion rate of the claim by stating that "[f]or post-cardiotomy shock start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute." *Label*, page 3. The FDA obtained this information from me and the other joint inventors.

DTX-10.1957. This paragraph recited some, but not all, of the statements from the Label relied upon by the Examiner—in particular, it did not include "refrigerating the diluted solution for up to 24 hours," which the Examiner cited as disclosing the

refrigerated storage limitation of then-pending claim 16. DTX-10.1874; DFF¶253; DTX-10.0616-618.

348. Kenesky then had an interview with the Examiner to discuss, in part, the draft declaration. DTX-10.1954. "The Examiner ***recommended*** amending paragraph 7 to include a reference to ***all of the subject matter from the FDA reference relied upon in the rejection*** and an unequivocal statement that one or more joint inventors invented all of the subject matter relied upon***, if possible***." *Id.* (emphasis added). Thus, the Examiner recommended that this information be added—she did not say it was required, and only that it be added "if possible." *Id.*

349. The revised, as-executed declaration stated, in part:

> 7. The Label discloses part of the subject matter of the claims, including a method of increasing blood pressure in a hypotensive human. The Label recites that, "[v]asostrict is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive . . . ." *Label*, page 1 (parentheticals omitted). The Label further recites a pharmaceutical composition for intravenous administration having 20 units of vasopressin per mL . . . ." *Label*, page 3. The Label further recites that the vasopressin formulation comprises "chlorobutanol [and] Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6." *Label*, page 6. The Label recites the infusion rate of the claim by stating that "[f]or post-cardiotomy shock start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute." *Label*, page 3. The Label recites refrigeration of the diluted vasopressin for up to 24 hours. *Label*, page 1. The FDA obtained this information from me and Matthew Kenney, as we invented this subject matter.

DTX-10.1937; Tr. 736:6-19 (Kannan). It thus added a reference to the statement from the Label that was missing from the draft declaration, along with a statement that "we [Kannan and Kenney] invented this subject matter." *Id.*; DTX-10.1874; DFF¶258. The statement does not say that Kannan and Kenney invented "all of the subject matter." *Id.*

350. The Examiner withdrew the rejection in light of the declaration because, among other things, it included a statement that the inventors of the then-pending claims "invented the subject matter disclosed in the FDA Label and relied upon in the rejection (¶6-7), and a reasonable explanation for the presence of the FDA as an author of the prior art disclosure (¶6, 8)." DTX-10.1967.

351. Defendants did not dispute at trial that the FDA obtained the subject matter of the Label indirectly from the inventors, through Par's regulatory department. DTX-10.1932-1934, 1967-1968; *see also* DFF¶251; DTDX-2 (Kannan 2019 Tr.) 258:10-18.

3. Inventorship

352. Defendants do not dispute Kannan's statement, in paragraph 6 of the declaration, that he and Kenney "invented" the "subject matter" of the then-pending claims, even though they did not invent every element recited in those claims (e.g., they did not invent and never claimed to have invented, for example, the use of vasopressin to treat hypotensive patients and the administration of vasopressin via intravenous injection). Tr. 514:14-515:10 (Cross); DTX-10.1937.

353. Nor do Defendants dispute that Kannan invented the portion of the Label concerning refrigeration of diluted vasopressin for up to 24 hours. DTDX-2 (Kannan 2019 Tr.) 254:19-25, 255:20-261:2; Tr. 712:19-713:15 (Kannan).

354. At his deposition, Kenney did not recall what work he contributed to the April 2014 Vasostrict Label. DTDX-3 (Kenney 2019 Tr.) 28:14-28:18, 29:7-13, 30:18-31:2, 44:11-15. Contrary to DFF¶262, this lack of present knowledge does not lead to an inference that he "did not invent or contribute to *any* of the subject matter of the April 2014 Vasostrict® Label." It is undisputed that Kannan and Kenney worked together on the studies and evaluation of refrigerated storage of Vasopressin, leading to FDA-approval of a longer, 24-month refrigerated shelf life for Original Vasostrict. Tr. 713:16-714:23 (Kannan). Further, the Examiner only requested a statement of inventorship by "one or more joint inventors." DTX-10.1954. Thus, Kannan's contribution alone would have been sufficient to satisfy the Examiner's request.

355. Further, and contrary to DFF¶263 and DFF¶266, Kannan never "admitted" he did not invent the subject matter of the Label. Kannan merely, and correctly, admitted at his deposition that he did not invent each individual element of the Label recited in Paragraph 7 of his declaration. DTDX-2 (Kannan 2019 Tr.) 252:3-254:25. He also readily admitted this at trial. Tr. 729:20-730:5. He has consistently testified that he understood that, just as he "invented" the "subject matter" of the then-pending patent claims (when he admittedly did not invent each individual element of those claims), his statement that he "invented" the "subject matter" of the Label refers to his contribution to the subject matter of the Label as

a combined whole, not an assertion that he "invented" each individual element of the Label. DTDX-2 (Kannan 2019 Tr.) 254:22-25, 255:10-18, 256:14-257:20, 260:22-261:2 ("As I mentioned before, my contribution was related to refrigerated storage. And as it states in the document, we invented the subject matter."); Tr. 716:9-718:17, 729:20-730:5 (Kannan).

356. Kannan credibly testified that he believed his declaration was true and accurate when he signed it. Tr. 716:24-717:16, 728:5-11 (Kannan). And properly understood, it was truthful.

357. Indeed, the Examiner recognized that Kannan did not invent each individual element of the Label, as it was well-known that vasopressin has been used in humans for over 100 years. Tr. 495:25-496:4 (Cross). Among other things, the Treschan and Russell references were prior art references before the Examiner that were prominent in the field with respect to the administration of vasopressin to humans. Tr. 509:25-510:7, 510:19-22 (Cross). The Examiner expressly found that these references disclosed all of the clinical limitations listed in Paragraph 7 of the declaration. DTX-10.1969; Tr. 514:14-516:24 (Cross).

358. Thus, as Defendants' expert (Dr. Cross) conceded during cross-examination, the Examiner recognized that the Par inventors did not invent, for example, the following elements from the Label recited in paragraph 7 of the declaration: the intravenous administration of vasopressin to treat hypotensive

patients, the use of vasopressin to treat patients suffering from vasodilatory shock, treating post-cardiotomy shock with a starting dose of 0.03 Units per minute, or treating septic shock with a starting dose of 0.01 Units per minute. Tr. 514:14-515:10 (Cross); DTX-10.1937, 1969.

359. Therefore, the evidence shows that the Examiner would not have and could not reasonably have understood the declaration as purporting to claim that the inventors had invented each individual element of the Label recited therein.[5] *See* Tr. 514:14-515:10 (Cross).

B. The Alleged Falsehood in the Inventorship Declaration Was Not Material to the As-Issued Claims of the '239 Patent

360. To the extent the Court finds that Kannan's statement that he "invented" the "subject matter" of the Label was incorrect, it should find that it was not unmistakably false. At worst, the statement lacked precision as to exactly what Kannan was claiming he invented and is subject to multiple interpretations, and Kannan credibly testified he believed it was true. *See* FOF356-359.

361. Defendants assert that the alleged falsehood was material to the prosecution of the '239 patent because the Examiner withdrew the Label as prior

[5] Defendants' citation to Dr. Chyall's testimony at Tr. 611:11-19 for the prospect that "the Examiner would not have issued the '239 Patent but-for the demonstrably false statements by Kenesky and Kannan to disqualify the 2014 Vasostrict Label as prior art" misses the mark. DFF¶276. Dr. Chyall's testimony related to criticality in view of the Label.

art based on the declaration and allegedly would have found the as-issued '239 claims unpatentable over the Label. *See* DFF¶276.

362. Even assuming that Kannan's inventorship statement was incorrect (which it was not), the alleged misrepresentation was immaterial to the as-issued claims of the '239 patent in any event, for at least three reasons:

363. First, under 35 U.S.C. § 102(b)(1)(B) (post-AIA), which applies here, a public disclosure made less than one year before a patent's effective priority date can be removed as prior art if it was made by "another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor." Thus, the relevant issue was whether the FDA "***obtained*** the subject matter" of the Label "directly or indirectly" from the inventors, not whether the inventors had "invented" that subject matter. 35 U.S.C. § 102(b)(1)(B) (emphasis added). This is consistent with the Examiner's recommendation that the statement about inventorship with respect to the Label be added, "if possible." DTX-10.1954. As noted above, Defendants do not challenge the veracity of Kannan's statements that he was a joint inventor of the pending patent claims and the FDA obtained the subject matter of the Label indirectly (via Par's Regulatory Department) from the inventors. FOF350-351. Thus, the Label was properly removed as prior art regardless of whether Kannan's statements about inventorship of the subject matter of the Label were true.

364. Second, the claims of the '877 Application were amended during prosecution in response to rejections over the other art, including PPC and Treschan. DTX-10.2211-2223. Specifically, the Examiner found the 0.01% SEQ ID after 4 weeks storage at 2-8ºC limitations of dependent claims 17-19 inherent in view of PPC with no further discussion, just as she did for the April 2014 Label. DTX-10.2217. Thus, the claims pending at the time of Kannan's November 2015 declaration were rejected anyway over other art. DTX-10.2211-2223.

365. The amendments removed the refrigerated storage limitation, and added, among other things, limitations reciting that the claimed vasopressin formulation has a pH of 3.5-4.1 and includes 0-2% vasopressin degradation products that were found in the allowed claims.[6] *See* DTX-10.2335; DTX-605.

366. The Label does not disclose the amount of impurities in Original Vasostrict, nor does it disclose the "0-2% vasopressin degradation products" limitation. DTX-30; Tr. 438:22-439:7 (Defendants' counsel), 442:14-443:7 (Park), 828:3-13, 846:1-23 (Kirsch). And Defendants admit that the degradation

[6] Any tacit implication by Defendants in DFF¶272 that the removal of claim limitations related to refrigerated storage somehow impacts Par's reliance on 35 U.S.C. § 102(b) is incorrect. Section 102(b) merely states that a public disclosure made less than one year before a patent's effective priority date can be removed as prior art if it was made by "another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor." 35 U.S.C. § 102(b)(1)(B). That requirement has been met and was not disputed by Defendants at trial. *See* FOF350-351, 363.

limitation is not inherently disclosed by the Label. Tr. 438:22-439:7 (Defendants' counsel) ("[H]e's not saying it's inherent."). Thus, it is undisputed that the Label does not anticipate the as-issued claims. *See* Tr. 710:1-16 (Defendants' counsel). Defendants have failed to prove that the Label would have invalidated the as-issued claims of the '239 patent. Tr. 846:1-23 (Kirsch).

367. Accordingly, even if the Label had not been removed as prior art, it would not have rendered the as-issued claims unpatentable, and therefore any alleged misrepresentation by Kannan relating thereto was not but-for material to the as-issued claims of the '239 patent. FOF362-366.

368. Third, the relevant disclosures were cumulative of the prior art before the Examiner, including Treschan, Russell, and overlapping pH ranges taught by various references (*see* discussion of Pitressin, PPC, etc. above, FOF191-196, 277). For example, Dr. Cross acknowledged that the Examiner found that all of the clinical limitations of the as-issued '239 claims were known, that Par never attempted to rebut those findings, and that the Examiner allowed those claims not because of any differences between the claims and the prior art relating to the clinical limitations. Tr. 509:3-19; 511:8-24 (Cross). Thus, he conceded that the prior art before the Examiner contain the same teachings concerning the clinical limitations as the Label. Tr. 516:6-11 (Cross).

C. There Was No Intent to Deceive

369. Kannan credibly testified that he believed that his declaration was true and accurate when he signed it, and that "subject matter" referred to "refrigeration of diluted vasopressin for up to 24 hours as a combination of all of the items stated in paragraph 7." Tr. 717:3-718:17, 728:5-11. This comports with Dr. Cross's testimony that the Examiner recognized that Par did not invent each individual element of the Label. Tr. 514:14-515:10 (Cross).

370. Intent to deceive is not the single most reasonable inference to be drawn from the evidence, because it is at least as reasonable to conclude based on the evidence that Kannan intended to convey that he invented the subject matter of the Label as a whole, including refrigeration of diluted vasopressin for up to 24 hours as a combination of all the items listed in paragraph 7 of his declaration, rather than claiming that he had invented each individual element. Tr. 717:3-718:17, 728:5-11 (Kannan). Moreover, as discussed above, no statement about inventorship of the Label was required to remove the Label as prior art, and the Examiner only requested that it be added if possible, so there was no reason for Par to add a statement that was not true. FOF363.

D. There Is No Immediate and Necessary Relationship Between the Alleged Inequitable Conduct and the Claimed Inventions of the '209 and '785 patents

371. There is no immediate and necessary relationship between the alleged falsity of the Inventorship Declaration and the '209 and '785 patents, because as detailed herein (FOF372-381) the removal of the Label as prior art is of no moment to those patents.

372. Par admits that the Label is prior art to the '209 and '785 patents; indeed, the Label discloses pH 3.4-3.6, which was believed in the prior art to be the optimal pH range, as discussed above (FOF196), and during trial, Defendants abandoned any assertion that the Label anticipated the Asserted Claims. Tr. 710:1-16 (Defendants' counsel).

373. The lack of an "immediate and necessary" relationship is made clear by the fact that, as detailed below (FOF374-381), (1) Par told the PTO during prosecution that the claims of the '785 and '209 patents were "narrowly drawn around the results of Examples 14 and 15 in the specification," which were disclosures added to those patents and not found in the '239 patent, and (2) the parties agree that the '785 and '209 patents are not entitled to claim priority back through the '239 patent to the '499 application.

374. In particular, the '239 patent was filed on May 20, 2015 and contained approximately 34 columns of disclosure. DTX-605.

375. The ’526 patent filed on October 10, 2016 as a continuation-in-part of the ’239 patent and added over 60 additional columns of disclosure, eight figures, and seven examples, including Example 14. *Compare* DTX-605 *with* JTX-001; Tr. 837:4-15 (Kirsch).

376. The ’209 and ’785 patents, in turn, were each filed on February 7, 2017 as continuations-in-part of the ’526 patent and added even more disclosure, including Example 15. *Compare* JTX-001 *with* JTX-002 *and* JTX-003; *see* Tr. 837:16-22 (Kirsch). Thus, there was significantly more data and information disclosed in the written descriptions of the ’209 and ’785 patents than that of the ’239 patent, including the data that supported the criticality of the claimed pH ranges of 3.7-3.9. Tr. 838:3-11, 838:20-839:3 (Kirsch).

377. Further, during prosecution of the ’785 and ’209 patents, Par stated that “the ***present specification*** provides data demonstrating the importance of the claimed pH of 3.7 to 3.9 in reducing the accumulation of impurities in a vasopressin formulation. The ***present claims are narrowly drawn around the results of Examples 14 and 15 in the specification***, which describe that a 20 U/mL vasopressin formulation prepared at pH 3.8 was tested for impurity levels over a 15-month study period.” *See* PTX-843 at PAR-VASO_0005816; PTX-844 at PAR-VASO_0009721 (emphasis added); Tr. 839:8-840:9 (Kirsch).

378. Par also stated that "Tables 53 and 54 [which were not included in the '239 patent] provide the results of the 15-month study. The Tables indicate that the pH fluctuated between 3.7 and 3.9 over the study period, and indicate that several of the impurities were vasopressin degradation peptides as described in Example 1 of the specification." *Id.*

379. Defendants do not dispute that the asserted claims of the '209 and '785 patents are narrowly drawn around the newly-added subject matter that was not included in the disclosures of the '239 patent and post-date the filing of the November 2015 Kannan declaration. *Id.*

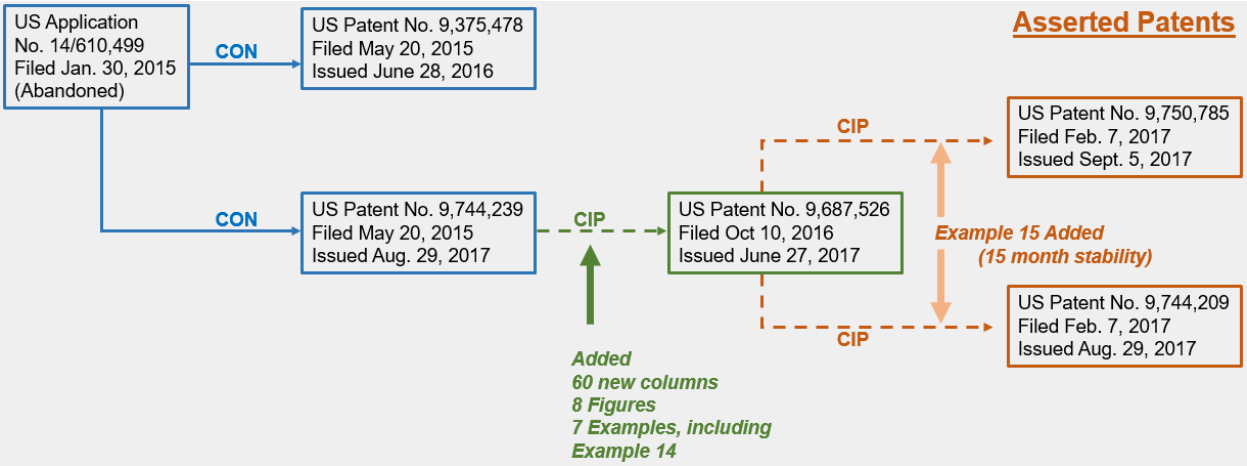
380. Indeed, the parties agree that the priority date of the asserted patents is February 7, 2017, the filing date of those patents, and Par is not claiming priority back to any earlier-filed application. Tr. 484:6-8 (Park), 806:20-23 (Kirsch); *Par v. Eagle* PTO Ex. 1 ¶¶ 27, 30; *Par v. Amneal* PTO Ex. 1 ¶¶ 29, 32.

381. Further, as discussed above, the Label teaches pH 3.4-3.6 whereas the claimed range is pH 3.7-3.9, and the Label does not disclose the 0.9-1.7% homologous impurities limitations. *See* FOF202-203.

VIII. INEQUITABLE CONDUCT THEORY II: DR. KANNAN'S PH DECLARATIONS

382. The two declarations underlying Defendants' second theory of inequitable conduct are Kannan's March 2016 pH declaration and his May 2017 pH declaration. *See* DTX-7.2159-2169; DTX-10.2352-2372. Those declarations were submitted during prosecutions, respectively, of the '478 and '239 patents—i.e., not in connection with the prosecution of either of the patents-in-suit. *Id.*

383. Indeed, the '478 patent is not even in the same priority chain as the patents-in-suit, because neither the '209 patent nor the '785 patent claimed priority back to it. *See generally* JTX-008; JTX-009. Dr. Kirsch used the following demonstrative to illustrate the relationships between the patents:



PDX6-57; Tr. 837:1-838:11 (Kirsch).

384. During prosecution of the '209 and '785 patents, the applicants argued the patentability of the pending claims based on the data and information described in Example 15 and elsewhere in the specification of those patents. *See* PTX-843 at

PAR-VASO_0005816-17; PTX-844 at PAR-VASO_0009721-22; Tr. 839:4-840:9 (Kirsch). The data for Example 15 post-dated the filing of the '239 and '478 patents, and hence it was not included in the disclosures for either of those patents. *See, e.g.*, DTX-605 ('239 patent).[7]

385. In particular, on June 28, 2017, Par filed Responses to Office Actions in connection with both asserted patents, making substantively identical arguments concerning the criticality of the claimed pH range. PTX-843 (submission in '209 file history); PTX-844 (submission in '785 file history). In both, Par explained that "[t]he present claims are narrowly drawn around the results of Examples 14 and 15 in the specification," with the results of the study described therein provided in Tables 53 and 54. PTX-843 at PAR-VASO_0005816; PTX-844 at PAR-VASO_0009721. Examples 14 and 15 describe 15-month stability data obtained on Par's Reformulated Vasostrict product, which had a pH of 3.8. *See* JTX-002 ('209 patent) at 101:60-107:38; JTX-003 ('785 patent) at 101:35-105:42.

386. The sub-title of the relevant section of the office actions responses was "The present specification establishes the criticality of pH 3.7-3.9 in limiting the amount of impurities in a vasopressin formulation." PTX-843 at PAR-VASO_0005816; PTX-844 at PAR-VASO_0009721. In that section, Par pointed

[7] As noted above, the '478 patent was a continuation of the '499 application, and thus shared a common written description with the '239 patent, which was also a continuation of the '499 application.

out that that the stability data from Example 15 supported the claimed impurity levels. *Id.* They further noted that this was consistent with Par's earlier, shorter-term pH studies. *Id.*

387. Par then pointed to the plot of the 40ºC impurity data from the earlier study and argued that it "further establishes" the criticality of the claimed pH range. *Id.*

388. Finally, Par argued that a POSA would not have recognized "the criticality of pH 3.7-3.9 in reducing the accumulation of impurities in a vasopressin formulation based on the cited [prior art] references because the cited references do not disclose the amount of impurities in a vasopressin formulation at pH of 3.7-3.9." PTX-843 at PAR-VASO_0005817; PTX-844 at PAR-VASO_0009722.

A. Kannan's March 2016 and May 2017 pH Declarations Are Not False

1. The Declarations Were Based on Earlier-Submitted Declarations by Inventor Sunil Vandse

389. During prosecution of the '478 patent, inventor Sunil Vandse submitted declarations reporting results from two pH studies: the first was reported in August 2015 and presented results from stability tests on vasopressin formulations with pH values from 3.5-4.5; while the second was reported in January 2016 and presented results from stability tests on vasopressin formulations with pH from 2.5-3.4. *See* DTX-7.1883-1884.

390. That declaration included several Figures plotting, respectively, the % Total Impurities and % Assay Decrease after 4-weeks storage at 25ºC and 40ºC. DTX-7.1887-1890 (Figures 1 and 2 (% Total Impurities); Figures 3 and 4 (% Assay Decrease)). It included Appendices with the raw data regarding pH values, time point of the measurement, temperature, and starting and ending values for assay and total impurities. DTX-7.1893-1896.

391. The declaration specifically explained that Figures 1 and 2 plotted the observed % total impurities values recorded during the studies (i.e., non-normalized plots), while Figures 3 and 4 plotted the % assay decrease, rather than the observed assay values (i.e., normalized plots), and that "[a]ssay is presented as a % assay decrease of vasopressin over the four-week study period, rather than absolute assay, because the amount of starting vasopressin varied between the Vasopressin pH 2.5 to 3.4 Formulations and the Vasopressin pH 3.5 to 4.5 Formulations." DTX-7.1885 ¶¶ 9-10.

392. Vandse was concerned with total impurities because he was interested in determining the lowest impurities at the end of the product's shelf life. DTDX-7 (Vandse 2019 Tr.) 176:17-177:7, 251:22-252:6.

393. Defendants do not assert inequitable conduct with respect to Vandse's January 2016 declaration.

2. The Kannan pH Declarations State that the Assay Plots Are Normalized, While the % Total Impurities Are Not

394. In reviewing the data and conclusions set forth in the Vandse declaration, the Examiner found that Figure 3—the plot of 25ºC % assay decrease—at pH 2.6-3.4 was "noisy and relatively constant" and that there appeared to be a "break" in the data, such that "it is not clear" if the difference in values "is significant or if it can be attributed to a difference associated with the two batches of experiments." DTX-7.2130[8] She then noted that "as with Figure 3," there also "appears to be a break in the data at pH 3.5" of Figure 1—the non-normalized plot of 25ºC total impurity values—that "may possibly be attributed to differences in the two experimental batches." DTX-7.2130-2131. She then commented that "because Figure 1 does not include error bars or statistical analysis it is not clear if the alleged differences due to pH are significant." DTX-7.2131. She then noted that the Figures plotting the 40ºC data "likewise lack a statistical analysis." *Id.*

[8] The Examiner refers to the "Vandse I" and "Vandse II" declarations in her rejection. *See* DTX-7.2130-31. "Vandse I" refers to Vandse's August 2015 declaration reporting the pH 3.5-4.5 experiments. DTX-7.618-625. "Vandse II" refers to Vandse's January 2016 declaration, which described both the earlier pH 3.5-4.5 study results, as well as a new pH 2.5-3.4 study and results. DTX-7.1883-1896. Because the Vandse II declaration contains all of the data and Figures from both pH studies, for ease of reference, Par refers to Vandse II as the "Vandse declaration."

395. Kannan's pH declarations were submitted to address these comments raised by the Examiner regarding the data in the Vandse declaration. Tr. 725:6-13 (Kannan); DTX-7.2140-2141. In his pH declarations, Kannan relied on the data and figures in Vandse's earlier-filed declaration—*see* March 2016 declaration, DTX-7.2162-2163, pointing to them by reference, and May 2017 declaration, DTX-10.2362-2365, reproducing them as Figures 5-8 of his declaration.[9]

396. Kannan addressed the Examiner's concerns by describing in detail how Par had taken pains to ensure that all of the test conditions and other variables that Par could control were kept constant as between the two pH studies. DTX-10.2367-2368 ¶¶24-28; DTX-7.2160-2162 ¶¶5-9.

397. For example, in his May 2017 declaration, he explained that both studies were prepared by the same scientist, in the same facility, using the same procedures. DTX-10.2367 ¶24; Tr. 724:14-726:22 (Kannan). Further, each solution contained "20 units/mL vasopressin in a 10 mM acetate buffer, adjusted to a specific pH with HCl" which "were then filled into 10 cc vials containing 10 mL solution each." *Id.*

[9] Figures 5-6 of the May 2017 Kannan declaration are the same as Figures 1-2 of the January 2016 Vandse declaration. *See* DTX-10.2362-2363 (Kannan); DTX-7.1887-1888 (Vandse). Figures 7-8 of the May 2017 Kannan declaration are the same as Figures 3-4 of the January 2016 Vandse declaration. *See* DTX-10.2364-2365 (Kannan); DTX-7.1889-1890 (Vandse).

398. Both sets of formulations "were stored for 4 weeks at 25ºC or 40ºC, in the same location and under the same conditions. The 25ºC samples of the pH 2.5 to 3.4 Vasopressin Formulations and the pH 3.5 to 4.5 Vasopressin Formulations were each stored in a stability chamber at 25°C and 60% relative humidity. The 40ºC samples of the pH 2.5 to 3.4 Vasopressin Formulations and the pH 3.5 to 4.5 Vasopressin Formulations were each stored in a stability chamber at 40ºC and 75% relative humidity." DTX-10.2367 ¶25; Tr. 724:14-726:22 (Kannan).

399. In addition, the analysis for each sample was performed in the same laboratory, "using the same, validated analytical methods, which include the same HPLC equipment configuration, and stationary and mobile phases," with intra-assay and inter-analyst precision within the acceptance criteria of the validated method. DTX-10.2367-2368 ¶¶26-28.

400. Dr. Kannan made the same statements regarding the variables held constant in his March 2016 declaration. DTX-7.2160-2162 ¶¶5-9.

401. By keeping all of these input variables constant between the pH 3.5-4.5 and pH 2.5-3.4 experiments, and only varying pH, Kannan concluded that "the differences in the assay (% label claim; vasopressin remaining) and % total impurities results for each formulation were attributable to changes in pH." DTX-10.2369 ¶ 32; DTX-7.2163 ¶ 16; Tr. 726:2-22 (Kannan).

402. With respect to the Figures discussed in his declaration, as first described by Vandse and repeated by Dr. Kannan, Figures 5-6 of the May 2017 Kannan declaration (Figures 1-2 from the Vandse declaration) plotted % Total Impurities at, respectively, 25ºC and 40ºC. DTX-10.2362-2363. Figures 7-8 (Figures 3-4 from the Vandse declaration) reported % Assay Decrease at, respectively, 25ºC and 40ºC. DTX-10.2364-DTX-10.2365.

403. Kannan stated that "FIGURES 5-6 provide ***direct comparisons of the % total impurities observed*** in the pH 2.5 to 3.4 Vasopressin Formulations with those observed in the pH 3.5 to 4.5 Vasopressin Formulations." DTX-10.2369 ¶ 29 (emphasis added); Tr. 721:2-17 (Kannan); *see also* DTX-7.2163 ¶ 13.

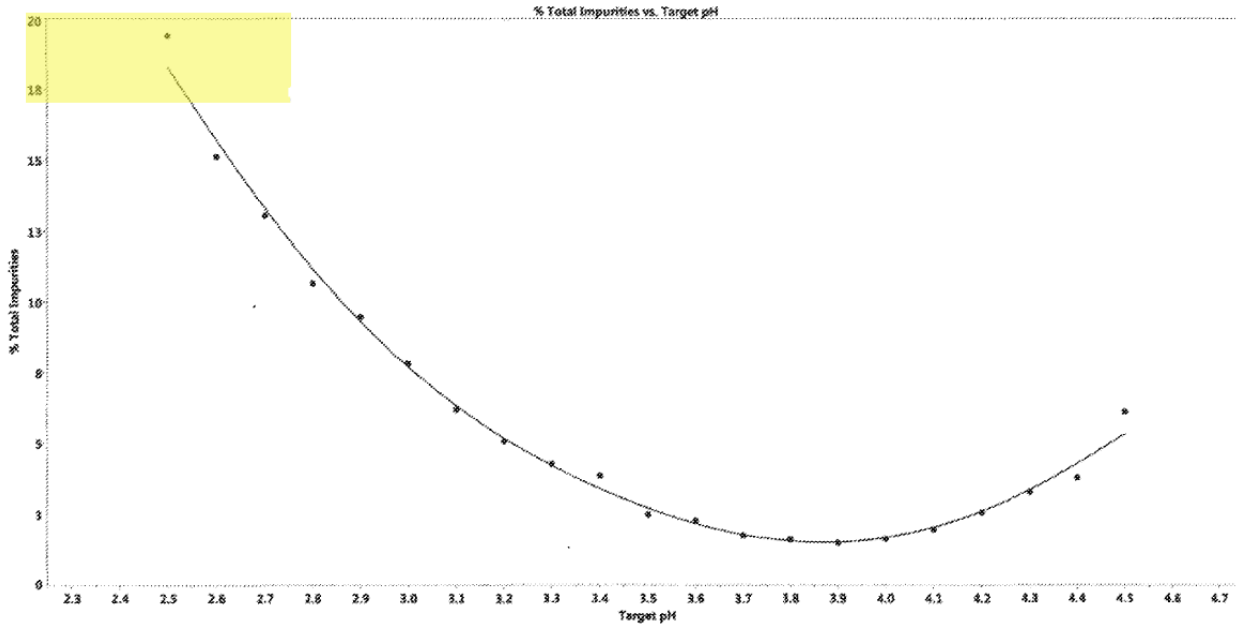
404. Kannan described the assay plots differently, stating instead that "FIGURES 7-8 provide ***normalized plots comparing the assay (% label claim; vasopressin remaining) observed*** in the pH 2.5 to 3.4 Vasopressin Formulations with those observed in the pH 3.5 to 4.5 Vasopressin Formulations." DTX-10.2369 ¶ 30 (emphasis added); *see also* DTX-7.2163 ¶ 14.

405. And he explained the reason for the difference: "The data were normalized and presented as % assay decrease of vasopressin over the four-week study period, rather than absolute assay, because the amount of starting vasopressin varied between the pH 2.5 to 3.4 Vasopressin Formulations and the pH 3.5 to 4.5 Vasopressin Formulations." *Id.*; Tr. 721:18-722:23 (Kannan).

406. By characterizing Figures 7-8 as "normalized plots" of the % decrease in observed assay values, while Figures 5-6 are not described as "normalized" and plot the total impurities values themselves, rather than % increases in total impurities over time, it would have been clear to the Examiner that Figures 5 and 6 were not normalized plots. As Dr. Kannan explained, it is readily apparent when looking at Figures 5-6 that they plotted the observed 4-week total impurities values themselves and were not normalized plots of that data. Tr. 723:10-724:13 (Kannan). The y-axis and title for Figures 5 and 6 are labelled as "% total impurities" (and not, for example, "% total impurities increase") which indicates that the plots are based on the measured impurity values themselves, not on normalized data. *Id.*; DTX-10.2362-2363. That is confirmed by comparing the measured values to the values plotted—e.g., the total impurities graphed at pH 2.5 in Figure 6 (DTX-10.2363) and the measured total impurities (not changes in total impurities) after 4 weeks, 40ºC at pH 2.5 shown in Appendix 1 of the Vandse declaration (DTX-7.1893):

NBD71-88-A	2.5	4	40C	81.89	19.41
NBD71-88-B	2.6	4	40C	87.33	15.60
NBD71-88-C	2.7	4	40C	89.36	13.46
NBD71-88-D	2.8	4	40C	91.98	10.98
NBD71-88-E	2.9	4	40C	93.08	9.78
NBD71-88-F	3	4	40C	94.33	8.09
NBD71-88-G	3.1	4	40C	96.61	6.39
NBD71-88-H	3.2	4	40C	95.61	5.25

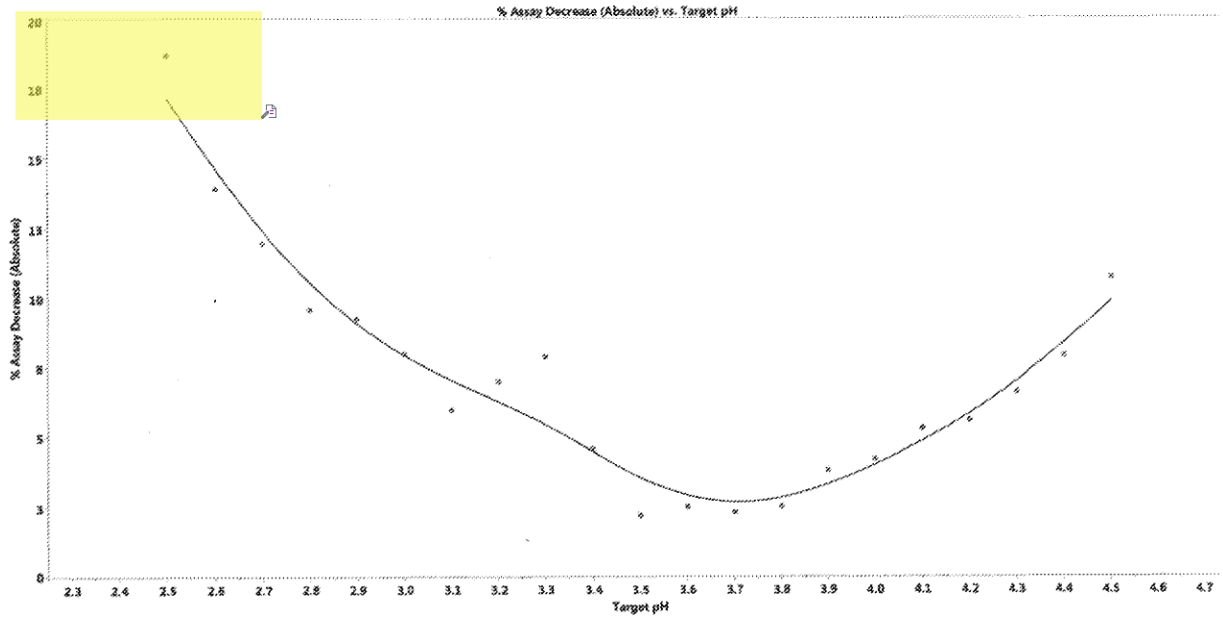
FIGURE 6



407. In contrast to Figures 5 and 6, the y-axes and title for Figures 7 and 8 are labeled as "% Assay Decrease (Absolute)." DTX-10.2364-2365. This references the decrease in assay, rather than the measured total % assay values themselves, which confirms that those Figures are showing "normalized" plots of the data. *Id.*; Tr. 724:7-13 (Kannan). As further confirmation, it is clear from looking at, for example, the % assay decrease graphed at pH 2.5 in Figure 8 (DTX-10.2365) and the starting and ending measured assay values at pH 2.5 in Appendix 1 of the Vandse declaration (DTX-7.1893), that the inventors were reporting % assay decreases (i.e., 100.57% - 81.89% = 18.68%) and not the measured assay values (i.e., 81.89%):

NBD71-88-A	2.5	0	40C	100.57	2.48
NBD71-88-B	2.6	0	40C	101.25	2.24
NBD71-88-C	2.7	0	40C	101.29	2.26
NBD71-88-D	2.8	0	40C	101.53	2.00
NBD71-88-E	2.9	0	40C	102.33	1.95
NBD71-88-F	3	0	40C	102.32	1.89
NBD71-88-G	3.1	0	40C	102.59	2.06
NBD71-88-H	3.2	0	40C	102.60	1.85
NBD71-88-I	3.3	0	40C	102.73	1.81
NBD71-88-J	3.4	0	40C	101.93	1.75
NBD71-88-A	2.5	4	25C	95.70	6.66
NBD71-88-B	2.6	4	25C	98.58	5.29
NBD71-88-C	2.7	4	25C	98.94	4.26
NBD71-88-D	2.8	4	25C	99.14	3.51
NBD71-88-E	2.9	4	25C	100.08	3.41
NBD71-88-F	3	4	25C	100.29	2.92
NBD71-88-G	3.1	4	25C	100.78	2.55
NBD71-88-H	3.2	4	25C	100.74	2.16
NBD71-88-I	3.3	4	25C	100.46	2.14
NBD71-88-J	3.4	4	25C	100.25	2.03
NBD71-88-A	2.5	4	40C	81.89	19.41

FIGURE 8



See also Tr. 575:17-576:4 (Chyall) ("And the bottom two charts, those concern the amount of Vasopressin that degraded upon storage at either 25 or 40 degrees C for the four-week storage period.").

408. At no time did Vandse or Kannan report that the Figures plotting total impurities data were normalized. DTX-7.2159-2169, 1883-1896; DTX-10.2352-2372.

3. The Kannan pH Declarations Correctly State that pH Is the Only Variable Not Normalized

409. Defendants assert that Kannan's statement in paragraph 32 of his May 2017 declaration that "as described above, … pH was the only variable that was not normalized" was false because the plots of the % total impurities values were not normalized. DFF¶¶300-302. But that assertion misrepresents what Kannan said in Paragraph 32. The cited statement did not indicate that, contrary to all of the above, Figures 5-6 were normalized plots; instead, it meant that, as Kannan had explained in detail above (*see* FOF395-401), all of the other "variables"—i.e., the inputs of the experiment—were held constant, not the output data (i.e., assay and impurities). Tr. 726:2-22 (Kannan).

410. As the Examiner would have recognized and understood, in response to her comments, Kannan did not submit new data or new plots, did not analyze or plot changes in impurity levels over time, or determine error bars for the data; instead, he provided a detailed explanation of how Par had done everything it could to keep everything the same between the two studies to the extent possible. *See* DTX-10.2367-2368 ¶¶ 24-28; DTX-7.2160-2162 ¶¶ 5-9; FOF395-401.

411. As explained in these paragraphs, the only input variable that Par could control which was not kept constant was pH. Kannan credibly testified that that was what he meant when he stated that "[a]s described above, … the only variable not normalized was pH." Tr. 724:14-726:22 (Kannan) ("[W]hen we talk about normalizing ***data***, we are treating the output data into, into some kind of mathematical equation to bring them to a common scale whereas when I'm talking about input ***variables***, normalized or not, I'm talking about whether that variable was kept constant or not.") (emphasis added).

412. Kannan believed that the statements in his declarations were true and accurate when he signed them, and that they still are. Tr. 725:2-726:22. Kannan also provided a reasonable explanation for why he and Vandse presented plots of % total impurities that were not normalized. *See* Tr. 722:24-723:9 ("As I specified earlier for the assay, the starting values were different between the two studies. Normalization was preferred to bring all the data into a common scale. However, that is not necessary for percent impurity because percent impurity is [already represented as] percent of amount of vasopressin in the, in the formulation. So there's no need to actually convert that into another normalized value."); *see also* DTDX-2 (Kannan 2019 Tr.) 274:24-276:13.

413. In their scientific discretion, Vandse and Kannan chose to present plots of the measured total impurities data itself, rather than normalized plots

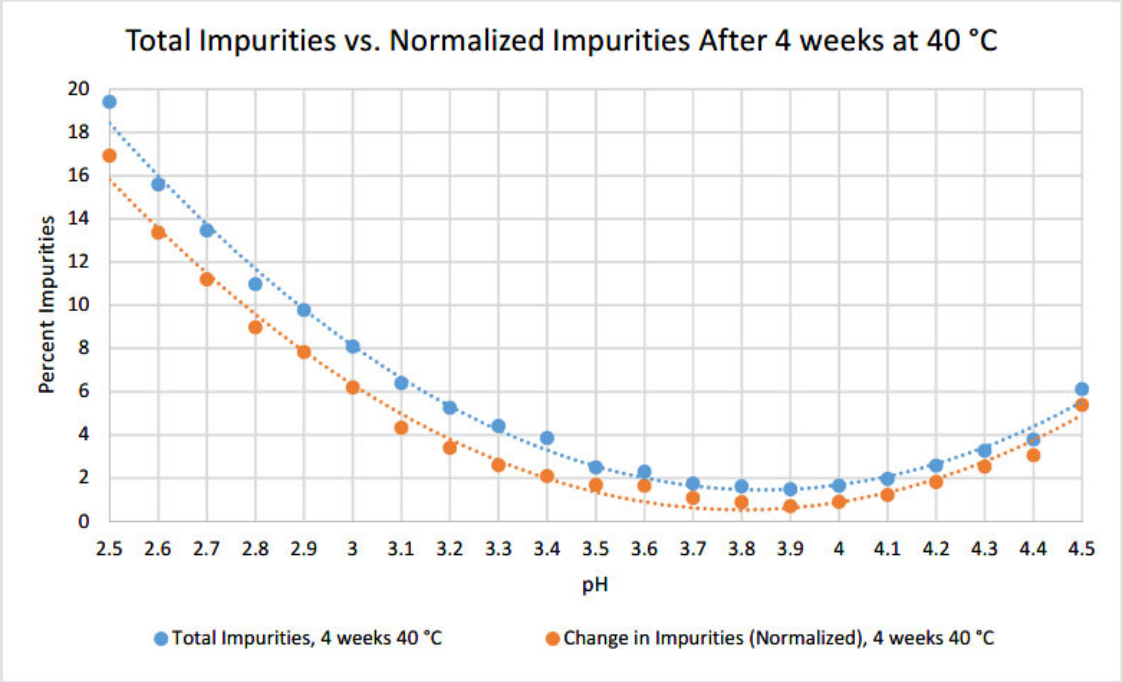
showing the change in total impurities values over time. FOF391-399. The fact that they did so was made clear by (1) their descriptions of the Figures (e.g., describing Figures 7-8 of the May 2017 Declarations, but not Figures 5-6, as "normalized plots"); (2) the labels on y-axes of the Figures (which for impurities referred to the total impurities values, rather than % increases in the total impurities values); and (3) comparison of the raw data to the values plotted in the Figures. FOF394-399.

414. In sum, all of the relevant data was presented to the Examiner, and there was nothing false, let alone unmistakably false, in Kannan's pH declarations. At worst, Kannan's statement that "[a]s described above, … the only variable not normalized was pH" had some ambiguity and could have more clearly stated that Kannan was referring to control of the input variables as between the two studies.

B. The Failure to Present Normalized Plots of the Total Impurities Data Was Immaterial to the Examiner's Evaluation of Patentability

415. Everyone who testified at trial agreed that evaluating the normalized plots of the total impurities data, rather than the non-normalized plots, would not lead one to reach a different conclusion regarding the criticality of pH 3.7-3.9 to stability as compared to the full-range of pH 2.5-45. Tr. 773:16-774:5 (Kirsch), 621:17-623:5 (Chyall), 727:18-728:4 (Kannan).

416. That is made abundantly clear by the following chart presented at trial (PDX6-14) comparing the normalized and non-normalized plots of the total impurities data at 40ºC:



Tr. 772:10-775:15 (Kirsch) ("The total impurities are the blue curve and the change in impurities are the red or orange curve and basically, they're parallel. So I mean, they show the same region of maximum stability whether you look at the total impurities four weeks, 40 degrees, or you look at the change in impurities, four weeks, 40 degrees.").

417. Indeed, Dr. Chyall ignored the comparison of non-normalized and normalized 40ºC plots altogether, and only testified that Dr. Kirsch gave too much weight to the 40ºC data, not that the non-normalized plot was different in any material way from the normalized plot. Tr. 604:13-25 (Chyall).

418. Defendants' citation to Kannan's testimony at his deposition that "[i]t may be possible" that the alleged "break" between the pH 3.4 and 3.5 in the plot of total impurities data at 25ºC was caused by differences in starting impurities (DFF¶305) is not to the contrary. Kannan only acknowledged that it is "possible," not that it is the only explanation or the correct explanation, and furthermore, Defendants denied Kannan access to the 40ºC data when answering this question, despite his explicit request to see it. DTDX-2 (Kannan 2019 Tr.) 287:10-287:25. Kannan said he was "not able to conclude one way or the other based on 25 degrees C data alone. I would like to see the 40 degrees C data also. . . . What I am trying to say is the extent of change at 25 degrees C will not be significant to see difference across the pH range. That's the reason I'm saying we would have to look at the 40 degrees C data also to make that conclusion." DTDX-2 (Kannan 2019 Tr.) 287:2-288:7.

419. Moreover, as Defendants themselves point out, "Examiner Bradley maintained her rejection and noted that ***both the impurities and assay plots*** presented in Vandse II declaration included a 'break in the data' between pH 3.4 and pH 3.5." DFF¶289 (citing DTX-7.2120, 2130-31) (emphasis added). Thus, the plots of the assay data—which were indisputably normalized—exhibited the same "break" as the impurities plots. Tr. 723:25-724:13 (Kannan); DTX-7.1885 ¶¶ 9-10; DTX-10.2369 ¶¶ 29-30. It is therefore reasonable to conclude that

normalizing for the starting amount of impurities would not fully explain the "break" in the data between pH 3.4 and 3.5, and that the changes in total impurity values shown in the plots is attributable to the changes in pH. *See* DTDX-2 (Kannan 2019 Tr.) 274:24-276:13.

420. Regardless, as discussed in detail below and above, while the 25ºC impurity data is inconclusive on its own, the 40ºC data, whether viewed as "normalized" plots or not, establishes that the region of maximum stability is at pH 3.7-3.9. Tr. 773:16-774:5 (Kirsch); FOF415-416. Dr. Kirsch explained that at 40ºC, there were adequate time-dependent changes in the vials at different pHs to overcome any alleged differences that there might have been with respect to starting impurities. Tr. 774:12-25 (Kirsch). He also provided a credible reason for focusing on the 40ºC data over the 25ºC data, because "in order to make distinctions between the effects of pH, you need to see enough degradation that you can, that you can make distinctions, and the 40-degree data provides that level of degradation." Tr. 770:21-771:8 (Kirsch); *see also* FOF418 (agreement by Kannan). These types of accelerated stability studies—short-term studies at high temperature—are "very typical in the art." Tr. 770:21-771:2 (Kirsch).

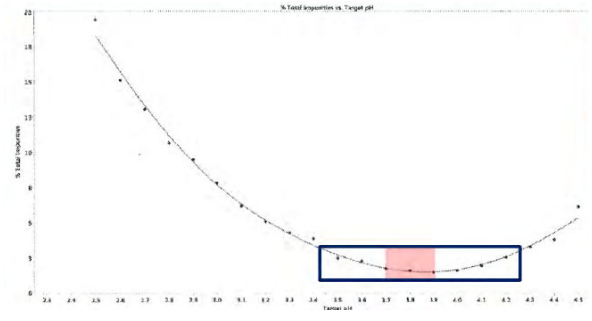
421. Dr. Chyall's contrary focus on the 25ºC data over 40ºC data was based on his conjecture that "there could be a change in mechanism of the degradation pathway" (Tr. 618:18-619:14), without any supporting evidence or

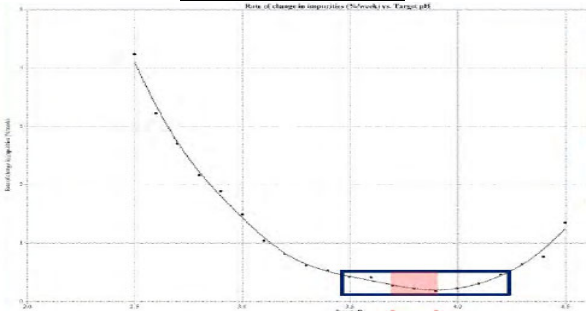
testimony to show that the degradation pathways would be different at 40ºC as compared to 25ºC. And Dr. Chyall conceded that accelerated stability studies (like the 40ºC studies) will enhance degradation, particularly for short-term experiments (Tr. 618:11-17). Dr. Kirsch's testimony is far more credible on this point, as even Dr. Chyall recognized that, compared to himself, "Dr. Kirsch has a lot more experience with peptides" (Tr. 620:13-16).

422. Accordingly, in alleging impropriety on the part of the inventors, Dr. Chyall's and Defendants' focus on the 25ºC impurity data, with minimal reference to the 40ºC data (*see* DFF¶308; Tr. 599:6-601:3 (Chyall)) is misguided. At best, the 25ºC plots that Dr. Chyall relies on show that, for four weeks at room temperature, a broad range of impurity values exhibit relatively low levels of impurities. Tr. 599:6-601:3, 621:7-623:5. The inventors said much the same thing to the Examiner. *See, e.g.*, DTX-10.2361 ¶ 17 ("The data in **FIGURE 5** shows the % total impurities after four weeks at 25ºC was lowest and most consistent in the range of pH 3.5 to 4.5.").

423. Indeed, what Dr. Chyall prepared but skipped over in his presentation is that the normalized and non-normalized data plots are remarkably similar at 40ºC. *Compare* DDX4-16 *with* DDX4-24 (annotations by Dr. Chyall):

"Non-Normalized" **"Normalized"**





See DTX-10.2363; DTX-79. Tellingly, Dr. Chyall drew a box around the same pH range (3.5-4.2) for both the normalized and non-normalized plots, indicating that he believed the "stable range" based on the inventors' impurity data included data points not claimed by the inventors. Tr. 579:20-580:15 (Chyall). This range is, importantly, similar to the stable range based on total impurities at 40ºC reported by the inventors. *See* DTX-10.2361 ¶ 17 ("The data in **FIGURE 6** show that the % total impurities after four weeks at 40ºC was lowest and most consistent in the range of pH 3.5 to 4.1."). As a result, there is virtually no daylight between Dr. Chyall's and the inventors' interpretation of the 40ºC impurity data.

424. As cited above (FOF416), Dr. Kirsch prepared and presented a chart at trial directly comparing normalized vs. non-normalized impurity data at 40ºC, something Dr. Chyall did not do for any of the data. This chart showed that the curve of best fit for the normalized and non-normalized impurities at 4 weeks at 40ºC showed the same region of maximum stability, a point Defendants did not dispute at trial. Tr. 772:10-775:15 (Kirsch).

425. Further, Dr. Kannan testified that the conclusions of his declarations would not have changed whether the impurity data was normalized or not. Tr. 727:18-728:4 (Kannan). Defendants latch onto a March 2016 email showing that inventors Kannan and Kenney exchanged graphs showing normalized plots of total impurities prior to the submission of the Kannan declarations, but that does not support an inference that anything nefarious happened here. DFOF¶301; DTX-66; DTX-67. In the email, Kannan asked Kenney whether the normalized graphs "make sense." DTX-66. The reasonable inference from the record presented at trial is that they decided, in their scientific discretion, that it made sense to simply refer in Kannan's March 2016 declaration to the plots previously presented to the Examiner in the Vandse declaration, rather than submitting new plots, since as Kannan and every expert has agreed, the normalized plots and non-normalized plots lead to the same conclusion. FOF408-417; *see also* DTDX-2 (Kannan 2019 Tr.) 274:24-276:13; DTDX-3 (Kenney 2019 Tr.) 176:3-176:12 (Q: If the starting impurities in different samples that were tested were different, why would you ever not normalize the data before comparing them? A. And I don't – I don't know what I would do in that situation. It would depend on how the data looks, if it would make sense to do that, do it that way.").

426. Since both sides' experts, as well as Dr. Kannan, agree that the presentation of the impurities data via normalized or not normalized plots would

not have impacted their conclusions, Par obtained no benefit from presenting non-normalized impurity plots as compared to normalized impurity plots to the Examiner. FOF415-416.

427. Thus, Defendants failed to present clear and convincing evidence that the normalized impurity plots, or the statement that "pH was the only variable not normalized," would have been but-for material to the patentability of the asserted claims—and indeed, the trial record demonstrates just the opposite, that the normalized plots of the total impurities data would have had no impact on the patentability of the as-issued claims of the '478 and '239 patents. FOF415-424.

C. There Was No Intent to Deceive

428. Kannan believed that the statements that "pH was the only variable that was not normalized" in his declarations were true and accurate when he signed them, and he credibly testified and provided his reasoning for why he still believes them to be true. Tr. 724:14-726:22.

429. Defendants interpret Kannan's statement as falsely stating to the Examiner that the plots of % total impurities, one of two items of measured output data and not an input variable that could be controlled, were normalized when they were not. DFOF¶¶300-302. Defendants' interpretation, however, ignores the clear statements by Vandse and Kannan in multiple paragraphs and Figures of their

declarations that the assay plots, but not the total impurity plots, were normalized. *See* FOF403-408.

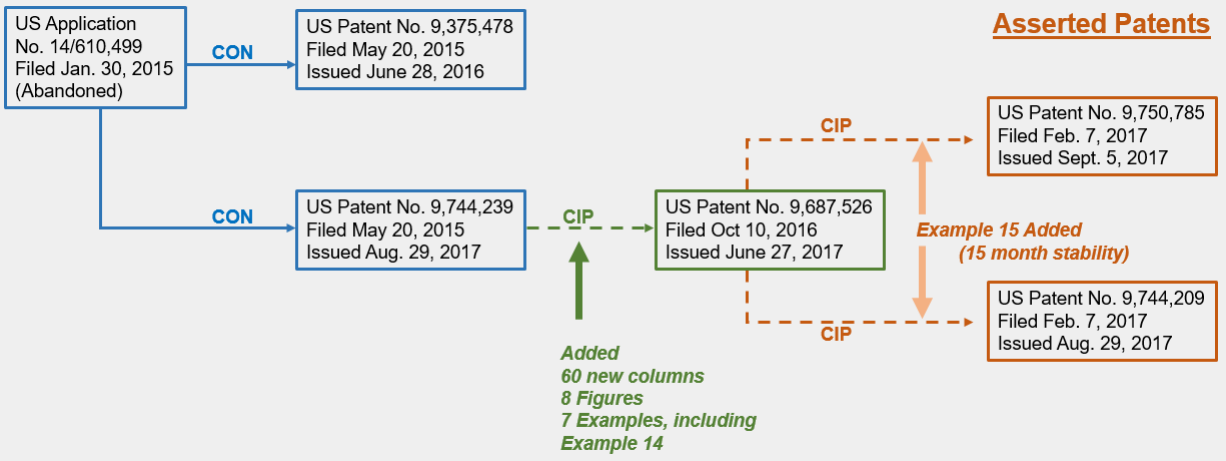
430. Additionally, Dr. Chyall agreed that he did not have "any information, any evidence that the inventors had deliberately withheld data" from the Patent Examiner, and Defendants presented no evidence at trial that anyone acted with intent to deceive the PTO by stating that "pH was the only variable that was not normalized" or by presenting non-normalized plots of the total impurities data, rather than the normalized plots of that data. Tr. 624:18-625:13. And even if Defendants' strained reading of Dr. Kannan's statement were a reasonable one, which it is not, it is not the only reasonable one. *See* FOF418-420. Indeed, it would make no sense to conclude, based on the evidence above, that Kannan and Kenesky intended to defraud the PTO by lying about normalization of the impurity data when there was no benefit to doing so.

D. There Is No Immediate and Necessary Relationship Between the Alleged Inequitable Conduct and the Claimed Inventions of the '209 and '785 patents

431. Even if the Court found that Defendants proved by clear and convincing evidence that the statement that "pH was the only variable not normalized" was false and that Kannan or Kenesky specifically intended to deceive the Examiner, the statement is of no moment to the prosecution or patentability of the '209 or '785 patents, as described herein.

432. The attenuation between the prosecution of the ’239 patent and the prosecutions of the ’209 and ’785 patents described above in Section VII.D applies with equal force here.

433. Further, the ’478 patent is not in the same priority chain as the ’209 and ’785 patents, because neither patent claimed priority to the ’478 patent. *See generally* JTX-008; JTX-009. Dr. Kirsch used the following demonstrative to illustrate the relationships between the patents:



PDX6-57; Tr. 837:1-838:11 (Kirsch).

434. Defendants assert that any alleged misconduct in connection with Kannan’s pH declarations, if proven, must necessarily carry through to render the ’209 and ’785 patents unenforceable, despite the declarations not being filed during prosecution of the ’209 or ’785 patents, because “the applicants relied on the same set of pH stability data generated from the March 2015 and November 2015 studies in prosecution of the Asserted Patents to demonstrate criticality of the

claimed pH of 3.7-3.9 over PPC." DFF¶318. This is conclusory and incorrect for the following reasons.

435. First, as discussed above, it is undisputed that the claims of the '209 and '785 patents are narrowly drawn around newly-added Examples 14 and 15. *See* PTX-843 at PAR-VASO_0005816-17; PTX-844 at PAR-VASO_0009721-22; Tr. 839:4-840:9 (Kirsch). Those Examples described pH and impurity data for FDA-submitted registration batches of reformulated Vasostrict and supported the patentability of the pending claims. PTX-843 at PAR-VASO_0005816; PTX-844 at PAR-VASO_0009721; Tr. 839:4-840:9 (Kirsch). The data reported in these Examples post-dated the filing of the '239 and '478 patents, and hence were not included in the disclosures for either of those patents. *See* DTX-605 ('239 patent).[10]

436. Second, consistent with Dr. Kirsch's testimony concerning the importance of the 40ºC data over the 25ºC data, the applicants pointed to the 40ºC plot from Figure 16 of the patents as confirmation that "further establishes the criticality of a pH close to 3.7 to 3.9." *See* PTX-843 at PAR-VASO_0005816-17; PTX-844 at PAR-VASO_0009721-22; Tr. 839:4-840:9 (Kirsch). And as discussed above, the normalized and non-normalized plots of the 40ºC impurity data are

[10] As noted above, the '478 patent was a continuation of the '499 application, and thus shared a common written description with the '239 patent, which was also a continuation of the '499 application.

essentially parallel, and hence indistinguishably different for purposes of patentability of the claimed inventions of the ’209 and ’785 patents. FOF415-417.

437. Third, the data relied upon from Figure 15 of the patents, which reflects the 25ºC data reported in the declarations, was cabined to the impurity data at pH 3.7-3.9, and thus did not implicate the alleged “break” in the data between pH 3.4 and 3.5. *See* PTX-843 at PAR-VASO_0005816 PTX-844 at PAR-VASO_0009721 (“[T]he total impurities in the vasopressin formulations stored at 25ºC for four weeks were not observed to exceed 1.6% between pH 3.7 and 3.9 based on visual inspection of Figure 15 of the specification as filed.”). Further, this data was used for the narrow purpose of showing that, after 4 weeks at 25ºC, the ***total*** impurities did not exceed 1.6% at pH 3.7-3.9. *Id.* That statement is indisputably true, and normalizing the plots in the manner suggested by Defendants would have no impact on that assertion, as it would plot changes in the impurity levels over time, not the % total impurities themselves, which is what Par was pointing to. *Id.*

438. Thus, Kannan’s statement that “pH was the only variable not normalized,” even if found to be false and intended to deceive the Examiner, had no impact on the patentability of the claimed inventions of the ’209 and ’785 patents. FOF431-437.

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Respectfully submitted,

FARNAN LLP

/s/ Michael J. Farnan
Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
919 North Market St.
12th Floor
Wilmington, DE 19801
Tel: 302-777-0300
Fax: 320-777-0301
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Attorneys for Plaintiffs Par Pharmaceuti
Inc., Par Sterile Products, LLC, and End
Par Innovation Company, LLC

OF COUNSEL:

Martin J. Black
Sharon K. Gagliardi
Brian M. Goldberg
Luke M. Reilly
Daniel R. Roberts
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
Tel: (215) 994-4000
martin.black@dechert.com
sharon.gagliardi@dechert.com
brian.goldberg@dechert.com
luke.reilly@dechert.com
daniel.roberts@dechert.com

Robert D. Rhoad
DECHERT LLP
502 Carnegie Center, Suite 104
Princeton, NJ 08540-7814
Tel: (609) 955-3200
robert.rhoad@dechert.com

Jonathan D. J. Loeb, Ph.D
DECHERT LLP
2400 W. El Camino Real, Suite 700
Mountain View, CA 94040-1499
Tel: (650) 813-4995
jonathan.loeb@dechert.com

Blake B. Greene
DECHERT LLP
300 W. 6th Street, Suite 2010
Austin, TX 78701
Tel: (512) 394-3000
blake.greene@dechert.com